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Original Articles by

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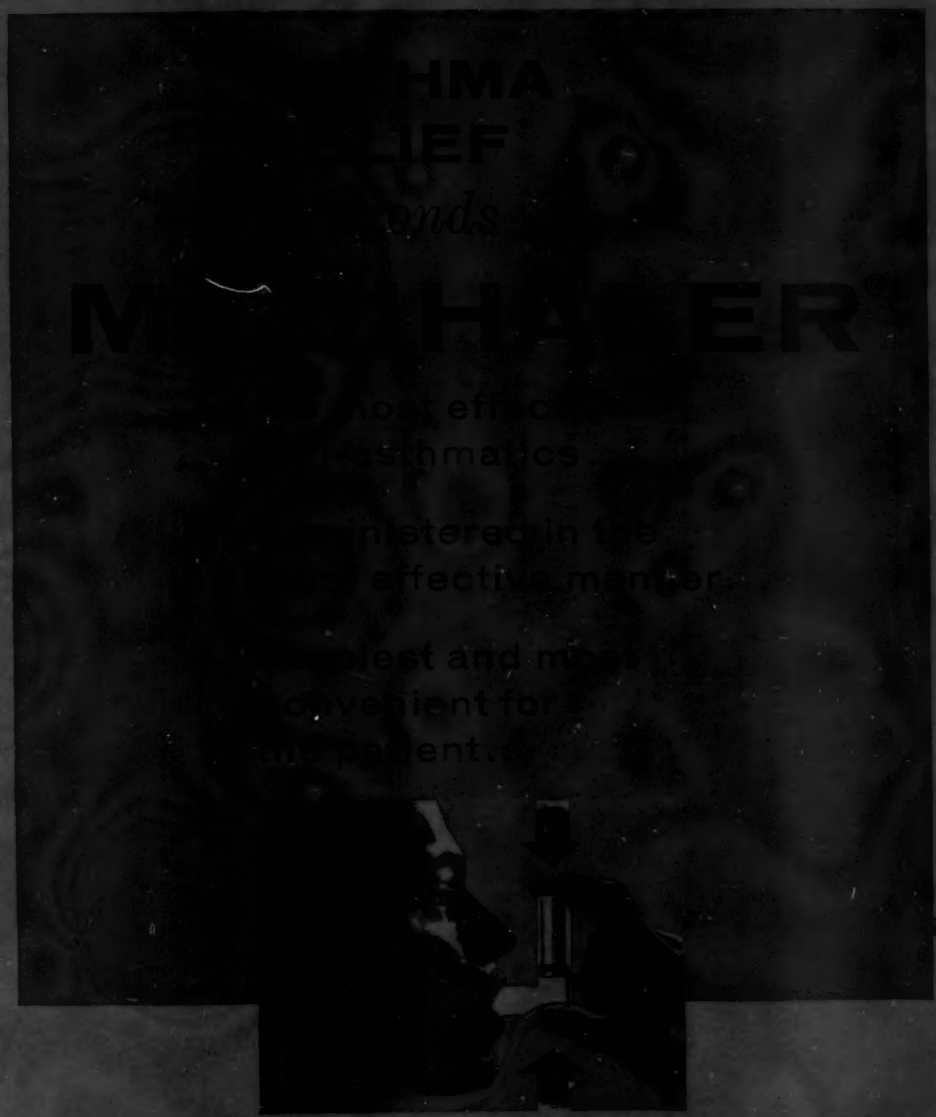
REPORTS OF THE COMMITTEE ON PUBLIC HEALTH

NEW YORK HEART ASSOCIATION



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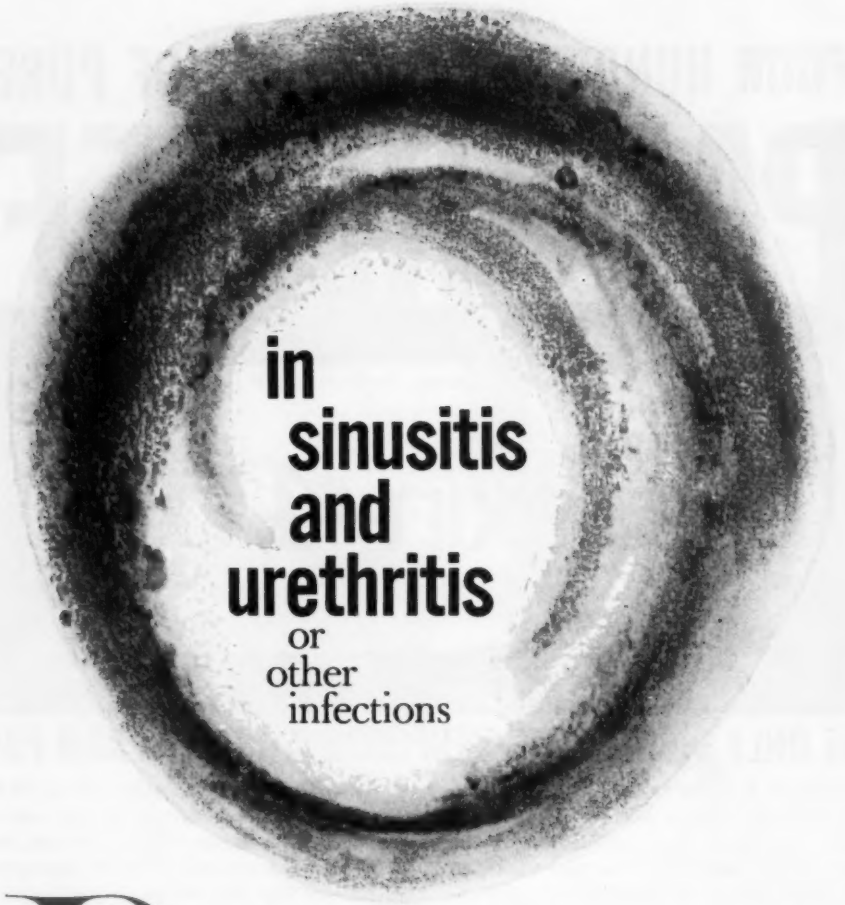

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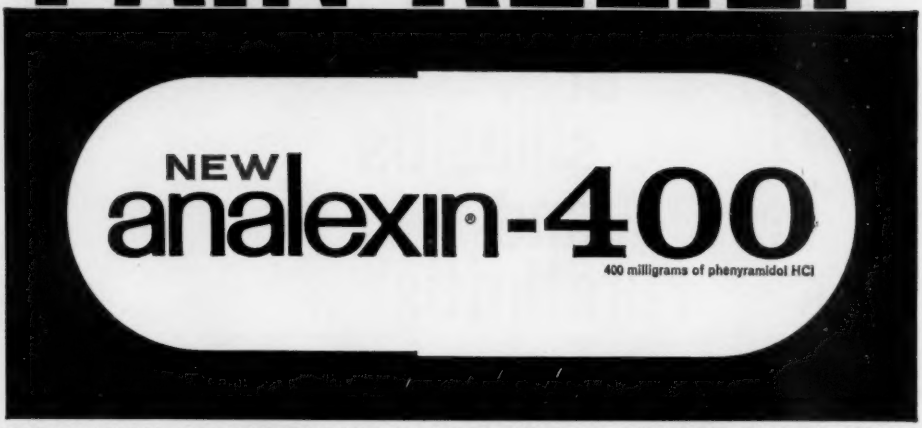

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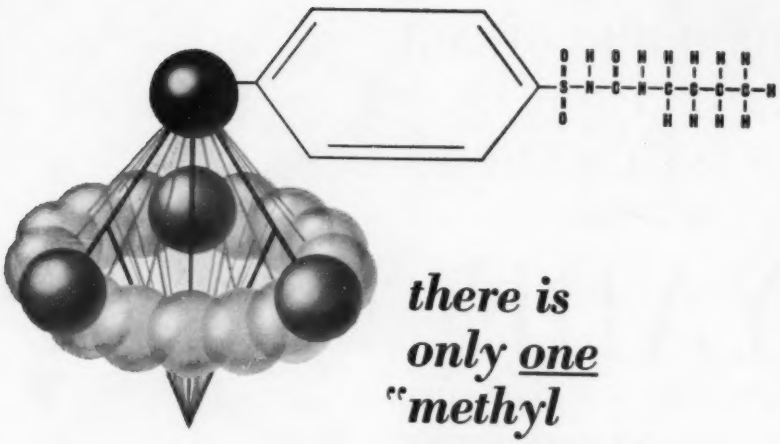

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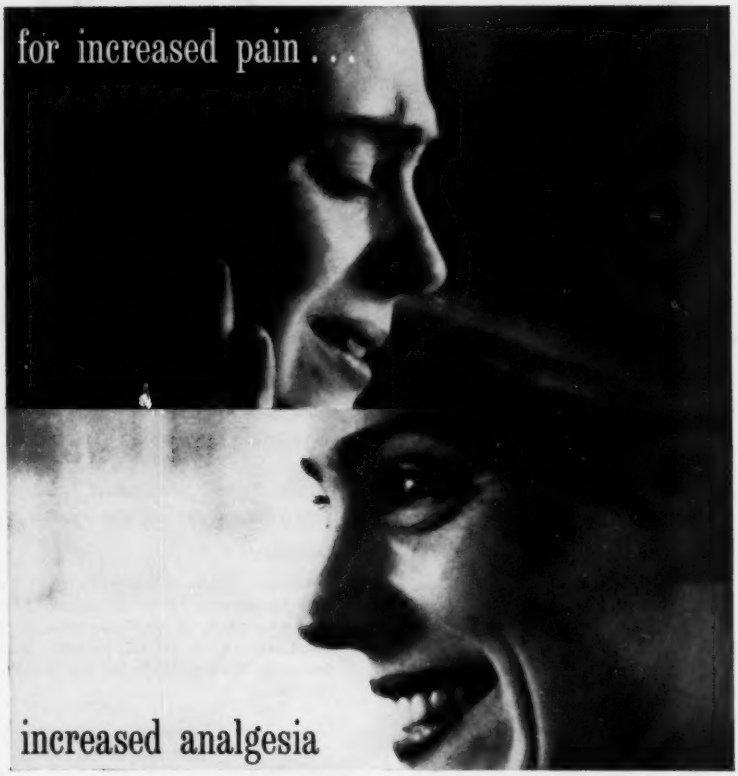

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BULLETIN OF
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MUSCULAR DISEASE*

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SKELETAL muscle dysfunction may result from impairment of any part of the path taken by the stimulus for voluntary movement (the motor unit), from the highest cerebral centers to the motor cortex, corticospinal tract, motor nuclei of the brain stem and anterior horn cells of the spinal cord, peripheral motor nerves, neuromuscular junction and muscle fibers (Table I). The manifestations of muscle dysfunction are limited. Weakness occurs in almost all disorders of the neuromuscular system, and is usually the presenting complaint. Weakness is accompanied by muscular wasting in diseases of the lower motor neurone (anterior horn cells and motor nerves) and in primary diseases of muscle. It is accompanied by stiffness or spasm in diseases of the upper motor neurone (motor cortex and corticospinal tract) or extrapyramidal system, and in poliomyelitis, tetany, tetanus, myalgia, scleroderma, and occasionally myositis. Weakness is accompanied by muscle pain or tenderness in poliomyelitis, tumor, disk, trichinosis, myalgia, paroxysmal

* Presented at the Fourth Annual Postgraduate Week, *Frontiers of Medicine and Surgery* of The New York Academy of Medicine, October 27, 1960.

This study was supported by Grant B-2093 from the National Institute for Neurological Diseases and Blindness, U.S.P.H.S., and Grant U-1025 from the Health Research Council of the City of New York.

TABLE I.—CAUSES OF SKELETAL MUSCLE DYSFUNCTION

Central Nervous System	
Emotional	
Upper motor neurone	vascular, infections, tumor, trauma, demyelinating and hereditary
Extrapyramidal motor system	
Cerebellum	
Lower motor neurone	
Anterior horn cells: polio, progressive muscular atrophy, syringomyelia, myelitis, tumor, disk, trauma	
Nerves: peripheral neuritis (*infections:* mononucleosis, polyneuritis, herpes zoster; *toxins:* diphtheria, lead, arsenic; *deficiency:* thiamine, nicotinic acid, B_{12}; *metabolic:* porphyria, amyloidosis; *vascular:* periarteritis, tumor, disk, trauma	
Neuromuscular Junction	
Chemical agents: depolarizing (acetylcholine, anticholinesterase, decamethonium, succinylcholine), competitive (d-tubocurarine)	
electrolyte concentration of plasma or muscle affecting neuromuscular junction, muscle or nerve: low or high K^+, Ca^{++}, Na^+, Mg^{++}	
Toxins: botulinus, tetanus, venoms	
Disease: myasthenia gravis	
Muscle	
Infectious and debilitating diseases: trichinosis, myalgia, other "Mesenchymal" tissue diseases: dermatomyositis, myositis, scleroderma, lupus, periarteritis	
Endocrine diseases: hyper- or hypofunction of thyroid, adrenal cortex, anterior pituitary, parathyroid	
Unknown cause: muscular dystrophy, myotonic dystrophy, myoglobinuria	

myoglobinuria, and some instances of peripheral neuritis and myositis. Weakness is associated with abnormal movements such as fasciculations in progressive muscular atrophy, anticholinesterase poisoning, and occasionally in syringomyelia or hyperthyroidism, and by grosser abnormal movements in some diseases of the extrapyramidal system and in tetany and tetanus.

The many causes of muscle dysfunction may be considered in the order in which they affect the passage of the motor stimulus, beginning in the frontal cortex and terminating in the muscle fibers.

CENTRAL NERVOUS SYSTEM

Emotional disorders. The impulse for voluntary motor activity arises in the frontal cortex and any impairment in volition may result in symptoms of weakness or fatigue. This may take the form of local weakness

or paralysis as in hysteria, generalized weakness and fatigue as in neurasthenia, weakness with catatonia as in schizophrenia, or weakness with wasting as in anorexia nervosa. Weakness or fatigue of emotional origin is frequently accompanied by a general increase in muscle tension associated with anxiety, and by incomplete muscle relaxation during rest or sleep. The increased muscle tension may result in pain in the back of the neck or head, headache, postural deformity, backache, pain in and around joints simulating rheumatism, and even generalized muscle soreness. The diagnosis of weakness or fatigue of emotional origin can be made only after careful exclusion of the many other causes of weakness, but is often suggested by a history of anxiety and increased muscle tension, fatigue on awakening, early evening drowsiness, and improvement in symptoms following suggestion or placebo administration. More than one-fourth of all patients referred to our clinic with the diagnosis of myasthenia gravis or other disease of the neuromuscular system have proved to have weakness of emotional origin. This has been much more common in women than in men. However, it must be kept in mind that weakness of emotional origin may be superimposed on weakness due to other cause, and the distribution of the weakness of emotional origin is sometimes determined by an underlying loss of function. In such instances, the major part of the disability may be relieved following hypnosis, placebo or other forms of suggestion, but evidence of the underlying disease process remains.

Upper Motor Neurone. Injury to the motor cortex or the pyramidal tracts may result from vascular disease (thrombosis, hemorrhage, or embolism of cerebral or spinal vessels), infection (encephalitis, meningitis, abscess, syphilis), disseminated sclerosis, pernicious anemia, amyotrophic lateral sclerosis, or brain or spinal cord tumor. An upper motor neurone lesion can usually be identified by its characteristic manifestations: weakness on the side of the affected pyramidal tract, with spasticity which is greater in the flexors of the upper extremities and in the extensors of the lower extremities, exaggerated tendon reflexes, diminished abdominal and cremasteric reflexes, clonus and extensor plantar reflex.

Lower Motor Neurone. Injury to the motor nuclei of the brain stem, to the anterior horn cells of the spinal cord, or to the anterior roots or motor nerves, results in the characteristic manifestations of a lower motor neurone lesion: weakness or paralysis of the muscles innervated

by the affected neurones, accompanied by diminished tone, softness and wasting, and dimunition or loss of tendon reflexes. Slow degeneration of the anterior horn cells, as occurs in progressive muscular atrophy and occasionally in syringomyelia, disk or spinal cord tumor, results in fascicular twitching of muscle.

Neuromuscular Junction and Muscle Membrane

Relatively little is known of the chemical influences affecting function of the central nervous system and peripheral nerves, but some information has accumulated concerning the effect of chemical agents on muscle excitation and contraction. Muscle appears to need an optimal concentration of acetylcholine (ACh) released for motor nerve endings, and of intracellular and extracellular concentration of potassium, calcium, sodium and magnesium ions for excitation and contraction, and of thyroid and adrenal cortical hormones for contraction. Too low or too high a concentration of any of these substances results in muscle dysfunction and weakness.

Normal neuromuscular transmission. Resting muscle fibers normally have a potential difference of approximately 90 mv. between the two sides of the surface membranes, the inner surface being negative with respect to the outer. They are therefore said to be in a state of "polarization". When a nerve impulse reaches the motor nerve endings, ACh, the normal mediator of neuromuscular transmission, is released. This compound becomes adsorbed to receptor substances of the muscle end-plate, following which the permeability of the end-plate region for sodium and potassium ions increases temporarily, resulting in movement of sodium ions into the muscle, and a less marked exit of potassium.[1, 2] This causes a disappearance (actually a slight reversal) of the potential difference across the muscle membrane in the end-plate region, which is said to have become "depolarized".[3] This depolarization is propagated along the muscle membrane as a wave of increased negativity, termed the muscle action potential. This, in turn, initiates contraction of the muscle fiber. Shortly after ACh has initiated depolarization of the end-plate, it is hydrolyzed into acetate and choline by cholinesterase enzyme concentrated in the muscle at the end-plate region. The potential difference across the entire muscle membrane is then restored, i.e., repolarization occurs and the muscle is thereby made ready to be depolarized again.

Disturbance of neuromuscular transmission is usually due to either deficient or excessive action of ACh on the motor end-plate, or to the action of drugs, to changes in ionic concentration, or to disease which simulates these effects.[4, 5] Neuromuscular block may occur without any change in the resting potential of muscle membrane (nondepolarizing block), or during or following reduction in the resting potential (depolarizing block). It may be characterized descriptively in terms of whether or not it inhibits the depolarizing action of ACh and is reversible by ACh.

Nondepolarizing Blocking Agents

Neuromuscular block, without alteration in resting membrane potential, may result from deficient release of ACh from the motor nerve endings, or from inhibition of the depolarizing action of ACh on the motor end-plates.

Agents which inhibit release of ACh. The paralysis in botulism,[6] puffer poisoning,[7] and possibly poisoning by the Rocky Mountain wood tick, *Dermacentor andersoni*,[8] is believed to be due to prevention by these toxins of release of ACh from terminal nerve endings. In botulism, release of ACh from parasympathetic postganglionic nerve endings is also prevented, resulting in paralysis of smooth as well as voluntary muscle. The eye muscles are usually affected early, resulting in diplopia, ptosis, dilated and often fixed pupils, and blurring of near vision due to paralysis of accommodation. The bulbar muscles may be affected next, and finally the skeletal and respiratory muscles, resulting in difficulty in swallowing and speaking, generalized weakness and respiratory distress. There is also constipation and urinary retention. The weakness is unaffected by neostigmine administration. Patients with mild botulism recover in about two weeks. In former years patients severely ill with botulism almost invariably died. However, today, if patients are kept alive by the use of tracheotomy and artificial respiration, function may begin to return in 7 to 14 days, and recovery may be complete.

Block occurring without change in the resting potential of the muscle membrane, and reversible by ACh. The block produced by d-tubocurarine is of this type. This drug exerts its effect by competing with ACh for receptor sites at the end-plate, so that the resulting block has been termed "competitive".[9] This type of block is characterized by inhibition of the depolarizing action of injected ACh, and by reversal of the block following the injection of sufficient ACh or anticholin-

esterase compound.[4e]

Block not associated with any change in membrane potential, but not reversible by ACh. This type of block occurs several minutes after the exposure of frog muscles to ACh or other depolarizing compound, and persists even after recovery of the muscle membrane from the initial depolarization. It is attributable to the development of refractoriness of the motor end-plate to ACh, and has been termed "desensitization" block.[10]

Block associated with hyperpolarization or stabilization of the muscle membrane. The weakness of hypokalemia is probably due in part to this mechanism, resulting from an increase in the ratio of intracellular to extracellular concentration of potassium.[11]

Depolarizing Blocking Agents

When the end-plate region is in the depolarized state it is inexcitable. This type of block is produced by an excessive concentration of ACh, by anticholinesterase compounds, by choline, and in most animal species by decamethonium and succinylcholine. During the initial stages of neuromuscular block produced by these compounds there is abnormally prolonged depolarization of the muscle membrane, most marked in the region of the end-plate, and no inhibition of the depolarizing action of injected ACh or anticholinesterase compound; in fact, these intensify the block by their additive effect.[4c, e] However, the neuromuscular block persists after return of normal membrane polarity and changes its character, owing to the development of refractoriness of the end-plate to ACh.[10] The properties of this "desensitization" block, which has been ascribed to alteration of the receptor substances from an "effective" to a "refractory" state, vary to some extent with different depolarizing agents.

Myasthenia Gravis

This disease results in either transient or persistent weakness and abnormal fatigability. The initial manifestations are most commonly referable to the extraocular muscles. The initial symptom is ptosis in approximately 25 per cent of patients, diplopia in 24 per cent, blurring of vision in 3 per cent, weakness of legs in 13 per cent, generalized fatigue in 6 per cent, difficulty in swallowing in 6 per cent, slurred and nasal speech in 5 per cent, difficulty in chewing in 4 per cent, weakness

of arms, hands, neck or face, in each of 3 per cent, and weakness of trunk or shortness of breath in 1 per cent.[12a] The extraocular muscles are affected some time in the course of the disease in almost every patient, and many have several episodes of transient weakness before the disease becomes persistent. Muscle weakness occurs unilaterally or bilaterally and in almost all combinations of functional disturbance. The elevators of the lids and upward deviation of the eyes are usually most affected, and downward deviation least affected. Occasionally there is complete limitation of extraocular movement. When ptosis is present, the orbicularis oculi are also usually affected, resulting in weakness of closure of the lids. This may persist even after remission of other symptoms of the disease, and is a very helpful sign in distinguishing between ocular palsy of neurogenic origin, which is usually not accompanied by orbicularis oculi weakness, and that due to myasthenia gravis or primary muscle disease. In 20 per cent of patients with myasthenia gravis the disease remains localized to the extraocular muscles, except for concomitant involvement of the orbicularis oculi. In 80 per cent the disease progresses to involve numerous muscles and usually becomes generalized.

The course of the disease is variable. In the majority of patients there is gradual extension of the involved areas leading to a relatively steady state of weakness, which remains unchanged for many years, with the exception of moderate fluctuations in severity. The basic level of weakness is usually reached within the first three years after onset, most often within the first year. In patients who develop severe myasthenia, the average interval between onset of the disease and the first severe episode is eight months. This interval tends to be shorter in male patients, in whom the disease is likely to progress more rapidly than in females. Of 300 patients with generalized myasthenia gravis who have been followed for an average period of ten years, 30 per cent died of the disease three months to 25 years after onset, and 85 per cent of these within three years.[12a] Most patients who survived beyond three years were likely to continue with a chronic form of the disease for many more years. Of the entire group 13 per cent are in complete or nearly complete remission at the present time, 26 per cent have had some improvement since their first severe episode of weakness, 21 per cent are unchanged, and 10 per cent have become worse.

Symptoms of the disease tend to fluctuate in severity from day to day, or at longer intervals, in almost all patients and approximately one-

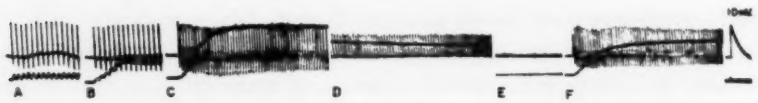

Fig. 1—Muscle action potentials and tension recorded from abductor of first finger of a normal subject in response to stimulation of ulnar nerve at a frequency of 5 per second (A); 10 per second (B); and 50 per second initially (C), for ½ minute (D), 1 minute (E), and following 15 seconds rest (F). Maximum tension (C) = 22 Kg.[5]

fourth have a remission lasting at least six months, with complete or nearly complete disappearance of signs and symptoms. In some patients mild ocular symptoms persist during the remission; in others these recur from time to time, particularly after emotional stress or upper respiratory infection. Most patients have only one remission, while 10 per cent have two to four. Half of the remissions begin during the first year of illness but others occur after as many as 17 years, with the average interval between onset of disease and remission being four years. The duration of remission varies up to 18 years, with an average of 4.6 years.

Mechanism of Neuromuscular Block in Myasthenia Gravis

Neuromuscular fatigue in normal subjects. When the ulnar nerve is stimulated, repetitively, by maximal stimuli at a frequency of 5 or 10 per second, the resulting muscle action potentials and tetanic twitch are sustained for several minutes. When the frequency of nerve stimulation is 25 per second, the muscle action potentials and tetanic twitch begin to decrease gradually in amplitude after about one minute of stimulation, with the tension diminishing more rapidly than the action potentials and returning more slowly after a period of rest (Figure 1). Therefore, following nerve stimulation, fatigue occurs in the neuromuscular junction and muscle fibers. The nerve fibers themselves are practically indefatigable.

Defect in neuromuscular transmission in myasthenia gravis. Stimulation at the same frequencies of the ulnar nerve of a myasthenic patient whose hand muscles are involved by the disease results in much more rapid decline in amplitude of the evoked potentials and tension than in normal subjects, with a characteristic biphasic course (Figure 2). There is no good evidence of a defect in muscle contractility in this disease and the manifestations of the disease appear to be due primarily to impair-

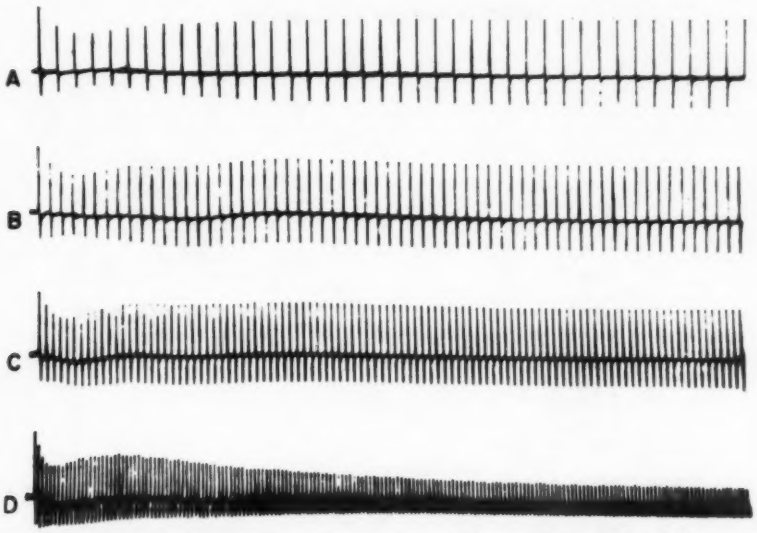

Fig. 2—The characteristic fall in muscle action potential response to repetitive nerve stimulation in a patient with generalized myasthenia gravis (S.P.). Stimulation frequency in A 5 per sec., in B 10 per sec., in C 25 per sec., and in D 50 per sec. The response to the initial stimulus measures 6.2 mV.[4b]

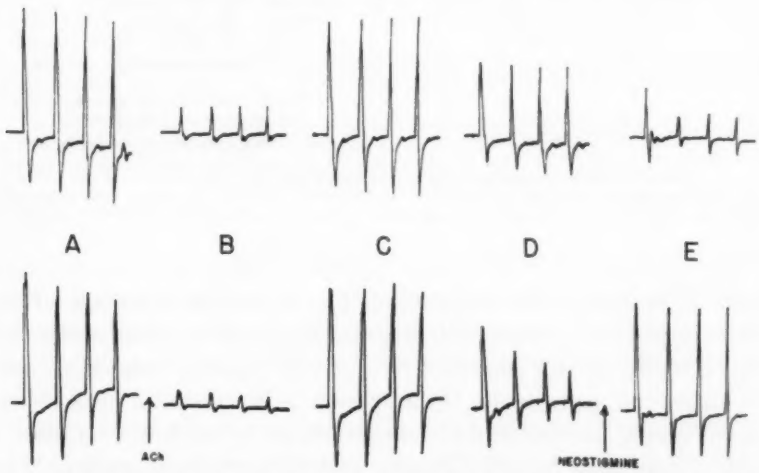

Fig. 3—Effect of ACh and neostigmine on the muscle action potential response to nerve stimulation in a normal subject (upper row) and a patient with myasthenia gravis (lower row). A, control response to four supramaximal nerve stimuli at 40 millisecond intervals; B, prompt depression 7 seconds after the intra-arterial injection of 5 mg. ACh; C, recovery 15 seconds after injection; D, late depression one hour after injection; E, effect of 0.5 mg. neostigmine, which produced further depression in the normal subject, and repair in the myasthenic patient.[12a]

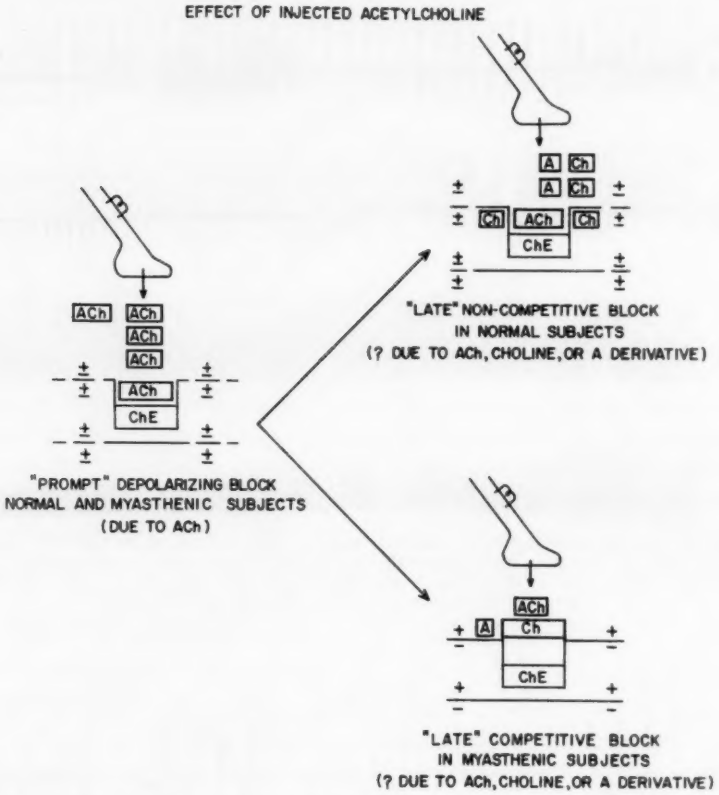

Fig. 4—Effect of ACh in normal subjects and patients with myasthenia gravis. Prompt depolarizing block occurred in both (left). This was followed by a late noncompetitive block in normal subjects and a competitive block in myasthenic patients (right).[12a]

ment of neuromuscular transmission. The impairment has many of the characteristics of a nondepolarizing and competitive (ACh-inhibitory) block, similar to that produced by d-tubocurarine in normal subjects. In myasthenic patients the block appears to be produced by ACh released during neuromuscular transmission, or by choline or a closely related compound formed following hydrolysis of the transmitter. The intra-arterial administration of either ACh or choline produces in most myasthenic patients a neuromuscular block which inhibits the depolarizing action of ACh and is reversed by ACh or anticholinesterase compounds.[4d] This competitive and presumably nondepolarizing block is

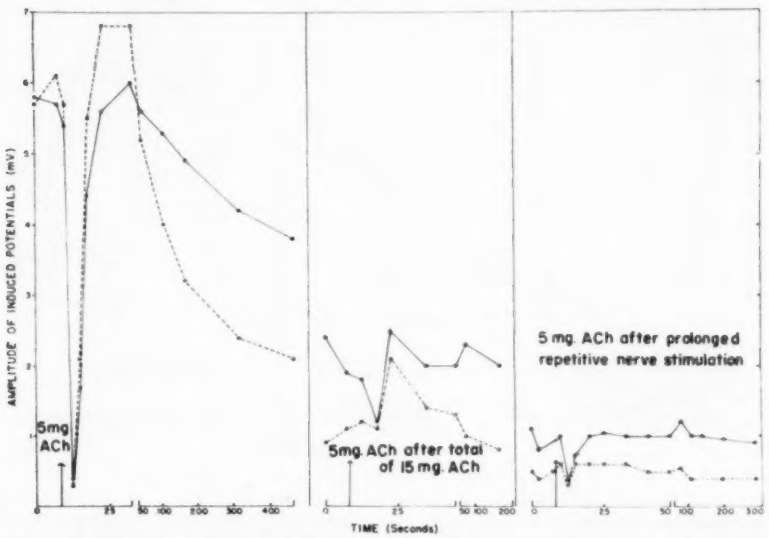
AMPLITUDE OF INDUCED POTENTIALS (mV)
5mg. ACh
5mg. ACh after total of 15 mg. ACh
5 mg. ACh after prolonged repetitive nerve stimulation
TIME (Seconds)

Fig. 5—Decrease in the prompt depressant and reparative action of ACh in a myasthenic patient as a result of the prior administration of ACh or prolonged repetitive nerve stimulation.

Left: Marked prompt depression and repair of first (●——●) and fourth (o - - - o) muscle action potentials (in response to a train of four nerve stimuli 40 msec. apart) following initial injection of 5 mg. ACh.

Middle: Much less prompt depression, and slightly less repair, when the same dose of ACh was administered after 3 prior injections of ACh, 16 minutes after the initial injection.

Right: Less prompt depression, and much less repair, when the same dose of ACh was administered on another day 23 minutes after repetitive nerve stimulation at 50/second for 75 seconds had resulted in a decrease in the amplitude of the potentials (from an initial amplitude of 5.8 and 5.2 mV.).[13]

in contrast to the predominantly noncompetitive and presumably depolarizing block produced by these compounds in normal subjects, in whom the impairment is intensified by ACh or anticholinesterase compounds (Figures 3 and 4). There is also some evidence of deficient release of ACh.[12b]

Different types of neuromuscular block in myasthenia gravis: the acetylcholine-insensitive state. In some myasthenic patients the block produced by the intra-arterial injection of ACh or choline inhibits the depolarizing effect of ACh, but is not reversed by ACh or anticholinesterase compounds.[13] Such a block, which resembles one stage of the effect of ACh in the frog,[10] may be termed ACh-insensitive. Patients

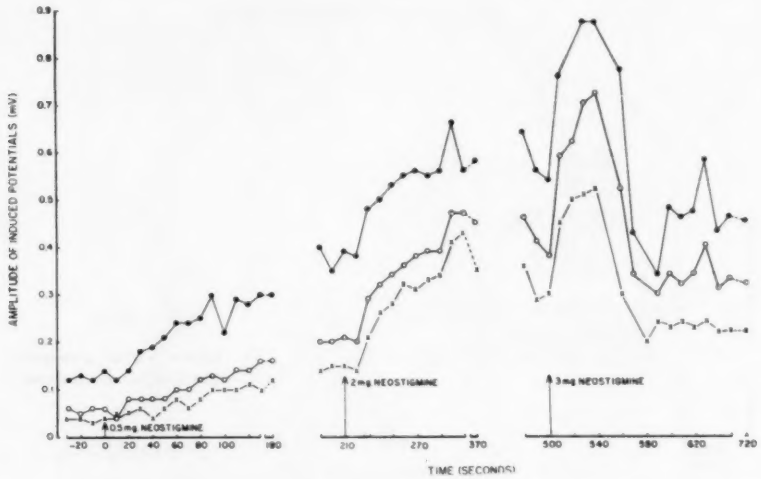

Fig. 6—Effect of successive intra-arterial injections of neostigmine on muscle action potentials in response to a train of 4 nerve stimuli (40 msec. apart) evoked every 10 seconds in a patient with very severe myasthenia gravis (H.W.). The first two injections produced partial repair, and the third, partial repair followed by depression.[41]

who manifest this type of block respond poorly or not at all to anticholinesterase medication; they are clinically ACh and neostigmine-insensitive. Patients in whom ACh produces the more usual ACh-reversible block may become ACh-insensitive during an exacerbation of their disease, or they may be rendered ACh-insensitive by the repeated intra-arterial administration of ACh or choline, or by prolonged repetitive nerve stimulation (Figure 5), which probably causes the local accumulation of endogenous ACh or choline.[13]

This ACh-insensitive state is probably responsible for the well-known clinical observation that while increasing doses of anticholinesterase medication result in increased strength in muscles affected by the disease, the maximal strength obtained is frequently far below normal. Further increase in dose of anticholinesterase compound does not result in any further increase in strength and excessive dosage may result in weakness, without passing through a stage of normal strength (Figure 6). The maximal level of strength obtained following optimal doses of anticholinesterase compound is lower during exacerbations of the disease, and may be lowered experimentally by the repeated intra-

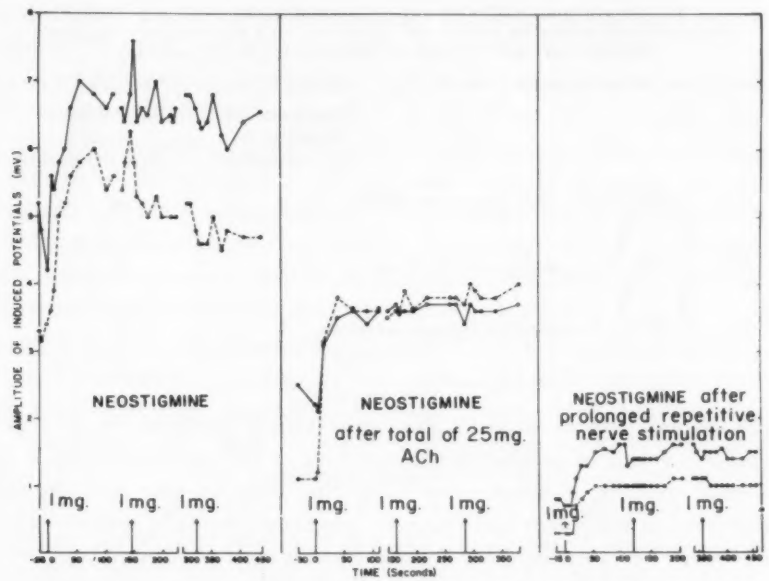

Fig. 7—Decrease in the reparative action of neostigmine in a myasthenic patient as a result of prior administration of ACh or prolonged repetitive nerve stimulation.

Left: Reparative effect of neostigmine on first (●——●) and fourth (o---o) muscle action potentials (in response to a train of four nerve stimuli 40 msec. apart).

Middle: When the same amount of neostigmine was administered on another day, after the prior injection of a total of 25 mg. of ACh had resulted in a decrease in the amplitude of the potentials (from an initial amplitude of 5.8 mV), there was less reparative effect, and the potentials did not approach their initial amplitude.

Right: When the same amount of neostigmine was administered on another day, 35 minutes after repetitive nerve stimulation at 50/second for 75 seconds had resulted in a decrease in the amplitude of the potentials (from an initial amplitude of 5.8 and 5.2 mV), there was even less reparative effect.[22]

arterial injection of ACh or choline or by prolonged repetitive nerve stimulation (Figure 7). At these times the patient is insensitive to ACh or anticholinesterase medication. It is this insensitive state that constitutes the main problem in management of the disease, and often leads to the administration of large doses of anticholinesterase medication and confusion as to whether the patient is overdosed (in "cholinergic crisis") or underdosed (in "myasthenic crisis"). Many patients who are thought to be overdosed are really in an insensitive state, and large doses of anticholinesterase compound often render the patient more insensitive.

While it is possible that the neuromuscular blocks occurring in

TABLE II.—POSSIBLE EVENTS AT THE NEUROMUSCULAR JUNCTION FOLLOWING COMBINATION OF ACETYLCHOLINE WITH VARIOUS FORMS OF RECEPTOR SUBSTANCE (R, R′, and R″)

	Inhibition of Action of ACh (ACh-Inhibitory)	Reversibility by ACh (ACh-Reversible)
ACh + R ⇌ ACh R → Depolarizing Block	−	−
ACh + R′ ⇌ ACh R′ → Competitive Block	+	+
ACh + R″ ⇌ ACh R″ → ACh - Insensitive Block	+	−

myasthenic patients may be due to abnormal products of ACh or choline capable of producing a competitive or ACh-insensitive block in normal subjects, it seems more likely that they are due to abnormal responses of the motor end-plates to substances normally released from the motor nerve endings. Myasthenic patients react abnormally not only to ACh and choline, but also to many other quaternary ammonium compounds, including decamethonium[4e, f, 14] and succinylcholine.[15a] In normal subjects decamethonium block of moderate degree does not inhibit the depolarizing action of ACh, and is not reversed by ACh or anticholinesterase compounds, while decamethonium block of marked degree does inhibit the action of ACh and is reversed by ACh or anticholinesterase compounds. In myasthenic patients, all levels of decamethonium block are reversed by ACh or anticholinesterase compounds.

It seems likely that depolarizing agents, including ACh released from the motor nerve endings, may combine with any of several forms of receptor substance in the motor end-plate, and that these combinations may result in at least three different types of block: 1) a depolarizing block which does not inhibit the action of ACh and is not reversed by ACh; 2) a competitive block which inhibits the action of ACh and is reversed by ACh; and 3) an ACh-insensitive block which inhibits the action of ACh but is not reversed by ACh (Table II). It is likely that mixtures of these types of block may occur, and that the predominance of one or the other may explain the clinical state of the myasthenic patient and his response to anticholinesterase medication. The disease may be due to the presence of abnormal forms of receptor substance, or to alterations occurring in receptor substance or in its combination

with ACh.[13] Abnormal muscle-binding serum globulins may be involved.[15b]

Anticholinesterase compounds used in the management of myasthenia gravis. The most useful of these are the quaternary ammonium compounds, neostigmine, pyridostigmine (Mestinon), and ambenomium (Mytelase). Bis-neostigmine (BC-40) and bis-pyridostigmine (BC-51, hexamarium) are longer-acting quaternary ammonium anticholinesterase compounds which require less frequent administration, but are less suitable for general use because of the danger of cumulation and overdose. Several organophosphorus anticholinesterase compounds have also had clinical trials in the management of myasthenia gravis. These have included di-isopropyl fluorophosphate (DPF), tetraethyl pyrophosphate (TEPP), octamethyl pyrophosphoramide (CMPA),[12a, 16] echothiophate (Phospholine), and sarin. While these compounds are more prolonged in their action than the quaternary ammonium compounds, and produce a more even and sustained increase in strength following the administration of only one or two doses a day, the danger of cumulation and overdose has precluded their general clinical use except under carefully controlled circumstances. The maximal strength obtained after optimal doses of any of these quaternary ammonium or organophosphorus anticholinesterase compounds is approximately the same.[12a] The compounds differ mainly in their duration of action (organophosphorus compounds > bis-neostigmine and bis-pyridostigmine > pyridostigmine and ambenomium > neostigmine), and in the severity of their parasympathomimetic side effects (organophosphorus compounds > bis-neostigmine and bis-pyridostigmine > neostigmine > pyridostigmine and ambenomium).

Management of overdose of anticholinesterase compound. In the management of myasthenia gravis, graded doses of an anticholinesterase compound are administered until a maximal level of strength is attained in the affected muscles. Unfortunately, in patients with severe myasthenia the maximal strength attained may be far below normal. Increasing doses may result in no further increase in strength, and excessive drug may produce generalized weakness, attributable to the accumulation of an excessive concentration of ACh at the motor end-plates and prolonged depolarization of this region, followed by refractoriness of the end-plates to ACh.[13] If overdose is suspected, the simplest procedure is to withhold medication for several hours and carefully observe

whether the strength increases or decreases. It is frequently helpful to observe the effect on the weakness of intravenous administration of the short-acting anticholinesterase compound edrophonium,[17] or of an oxime. The oximes pyridine-2-aldoxime methiodide (P-2-AM or 2-PAM), diacetyl monoxime (DAM), or 1, 1′ trimethylene-bis-(4-formylpyridinium bromide)-dioxime (TMB-4, EA1814) are capable of reversing neuromuscular block produced by anticholinesterase compounds in myasthenic patients, as in normal subjects.[18] The effect of this reversal depends on the prior action of the anticholinesterase compound, since neuromuscular function is restored toward its initial state. Whereas in normal subjects neuromuscular function and strength are returned toward normal, in myasthenic patients the effect depends on the status of the patient at the time of oxime administration. If sufficient anticholinesterase compound was administered to depress function, this is restored to a more optimal level, but if function was optimal at the time of oxime administration, it is restored toward the basal level present prior to the administration of anticholinesterase compound, i.e., it is depressed. Myasthenic patients suffering from anticholinesterase intoxication are therefore titrated with successive doses of oxime until strength is restored to the maximal level attained following the administration of optimal doses of anticholinesterase compound.

Unfortunately, many patients with severe myasthenia who are responding poorly to anticholinesterase medication fail to improve following either expectant management or administration of oxime or edrophonium, and they may become worse after any of these measures. The main difficulty in these patients is neither insufficient nor excessive anticholinesterase medication, but a refractory or "insensitive" state of the motor end-plates to the normal depolarizing action of ACh.[13] The only therapeutic measure available for this condition is to maintain respiration and reduce the dosage of anticholinesterase medication until response to this medication improves.[12a]

Myasthenic Syndrome With Carcinoma

Some patients with neoplasm, particularly small cell bronchogenic carcinoma, have muscular weakness and fatigue, most marked in the extremities.[19] The syndrome resembles myasthenia gravis in symptomatology, and usually in increased reactivity to d-tubocurarine and abnormal reactivity to decamethonium and succinylcholine. It differs

from myasthenia gravis in that only a minority of patients respond to neostigmine. Furthermore, the action potential and twitch evoked by a maximal nerve stimulus is much lower in relation to the strength of voluntary contraction than in myasthenia gravis, and the degree of facilitation during or after repetitive nerve stimulation is much greater. In some patients weakness has appeared many months before the tumor was noted, while in others it has followed the tumor. In some, evidence of peripheral neuropathy has occurred in the presence of neoplastic disease.

Alterations in Electrolyte Concentration

Alterations in concentration of potassium, calcium, sodium or magnesium in the extracellular fluid may result in derangement of excitation, not only of the motor end-plate, but also of the muscle fiber, nerve, and cardiac and smooth muscle.

Potassium. The normal resting potential of the muscle membrane is attributed mainly to the concentration gradient of potassium ions across the membrane; in experimental animals the resting potential varies with this gradient.[1] Hypokalemia may develop when there is deficient intake or absorption of potassium, excessive loss in vomitus, stool or urine, or excessive intracellular movement of the ion. The excretion of potassium by the distal tubules of the kidney, like the reabsorption of sodium, is under hormonal control. Aldosterone, cortisone, and desoxycorticosterone increase the tubular reabsorption of sodium and the excretion of potassium. The administration or excessive endogenous production of these hormones, as in aldosteronism or Cushing's disease, increases the excretion of potassium and may result in hypokalemia. Repeated administration of diuretics, such as mercurial diuretics, Diamox and Diuril (chlorothiazide), administration of sodium chloride, and increased protein catabolism, also increase the renal excretion of potassium. Renal tubular dysfunction may result in loss of potassium when the tubules are unable to secrete hydrogen or ammonium ions in exchange for reabsorbed sodium and must excrete potassium instead. Hypokalemia may also occur as a result of excessive movement of potasssium into cells of the liver following the administration of large amounts of glucose and insulin in the treatment of diabetic acidosis, into cells throughout the body in alkalosis, or into the muscle in periodic paralysis. This rare disorder, which is usually familial, is characterized by periodic attacks

of weakness. Onset of the disease is usually during puberty. Attacks almost always occur while the patient is asleep, four to nine hours after supper, particularly after a meal high in carbohydrate.

Hypokalemia due to any cause, if sufficiently severe, results in impairment of function of skeletal, cardiac, and smooth muscle. This is more likely to occur after rapid reduction in plasma potassium concentration than after gradual reduction. Weakness due to periodic paralysis occurs following less marked depression of serum potassium (usually to less than 3 mg. per cent) than that due to other causes of hypokalemia (usually to less than 2 mg. per cent) and is much more severe at comparable levels of hypokalemia. Weakness due to hypokalemia characteristically involves the muscles of one or all extremities, the trunk and neck, and sometimes the muscles of respiration. The muscles innervated by the cranial nerves are rarely affected. Both the tendon reflexes and the muscle contraction in response to direct percussion are diminished. The latter finding indicates that there is impairment of reactivity of the muscle fibers, and enables weakness due to hypokalemia (or hyperkalemia) to be differentiated from that due to peripheral neuritis, in which the direct muscle response to percussion is not affected despite disappearance of the tendon reflexes.

In normal subjects, rest or the administration of glucose, epinephrine, or potassium chloride causes the movement of potassium into muscle from the extracellular fluid.[11, 20] Exercise, the administration of large doses of insulin, deficient intake of potassium, excessive loss of potassium in vomitus, stool or urine, or alkalosis, causes the movement of potassium out of muscle. In patients with periodic paralysis, rest, glucose, insulin, or epinephrine causes an exaggerated movement of potassium into muscle. During attacks of periodic paralysis, exercise or the administration of potassium chloride is followed by an exaggerated movement of potassium out of muscle. The initial event during an attack of periodic paralysis is an abnormal uptake of potassium by muscle, induced by the prior ingestion of carbohydrate and by rest. This is followed by a decrease in reactivity of muscle to the depolarizing action of ACh. This finding is suggestive of an abnormal increase in muscle membrane potential (hyperpolarization of the muscle membrane) attributable to an abnormal increase in the intracellular to extracellular concentration ratio of potassium,[11] but confirmation awaits direct measurement of membrane potential. There is a decrease in

muscle responsiveness to nerve stimulation, in propagation of excitation and in contractility, resulting in paralysis. Following the administration of potassium chloride there is, first, a return of the extracellular concentration of potassium toward normal. This results in a return towards normal of reactivity to acetylcholine, and probably of the muscle membrane potential, owing to a return toward normal of the intracellular to extracellular concentration ratio of potassium. The partial return of muscle responsiveness, propagation of excitation, and contractility results in partial return of strength and increased muscle activity. This is followed by extrusion of potassium from muscle, and then by accelerated improvement in muscle function and strength. Conn[21] has reported that attacks of periodic paralysis are preceded by increased urinary excretion of aldosterone, decreased excretion of sodium, and movement of sodium into muscle. However, these changes are not present in most patients.

Hyperkalemia results mainly from deficient renal excretion of the ion, or from excessively rapid intravenous administration. The former usually occurs in association with anuria or oliguria and is seen particularly in acute renal insufficiency. Hyperkalemia of moderate degree may also result from adrenal cortical insufficiency, or from prerenal causes of reduced renal blood flow. Movement of potassium out of cells and into the extracellular fluid may occur as a result of intravascular hemolysis, tissue damage as in crush injury, or acute acidosis, and hyperkalemia follows, particularly if there is also impairment of renal function. Movement of potassium out of muscle into the extracellular fluid also occurs in a rare heritable disease, adynamia episodica hereditaria.[22] This is in many ways the opposite of familial periodic paralysis. Attacks of weakness occur during the day rather than at night and about one hour after exercise. There is slight to moderate elevation of serum potassium. Attacks of weakness may be precipitated by oral potassium administration, prevented by the prior administration of glucose, and relieved by the intravenous administration of calcium.

Hyperkalemia, if sufficiently severe, results in impairment of function of skeletal, cardiac, and smooth muscle. This is more likely to occur after rapid increase in plasma potassium concentration than after gradual increase. Weakness due to adynamia episodica occurs following less elevation of serum potassium (usually to more than 6 mg. per cent) than that due to other causes of hyperkalemia (usually to more than 9 mg. per cent). Weakness due to hyperkalemia clinically resembles

that due to hypokalemia, but the electromyographic and electrocardiographic alterations are different. Since the administration of potassium to normal subjects causes an increase in reactivity of muscle to the depolarizing action of ACh,[11] it is believed that the weakness of hyperkalemia may be due, at least in part, to a decrease in muscle membrane potential (depolarization), attributable to a decrease in the ratio of intracellular to extracellular concentration of potassium. It is believed that the occurrence of weakness in patients with periodic paralysis and adynamia episodica at levels of serum potassium not ordinarily associated with weakness is due to the reciprocal changes in potassium concentration occurring within the muscle. This would result in a greater change in the ratio of intracellular to extracellular potassium than occurs following depletion of body potassium, or administration of the ion, when the intracellular and extracellular concentrations would change in the same direction.

Muscle

DISORDERS OF THE ENDOCRINE GLANDS

Weakness may occur when there is either deficient or excessive function of the thyroid, adrenal cortex, anterior pituitary or parathyroid glands. It may also occur in hypoglycemia due to any cause.

Hyperthyroidism. About 70 per cent of patients with hyperthyroidism have some degree of muscular weakness. When this is severe and associated with muscular wasting, the term thyrotoxic myopathy has been applied. The symmetrical wasting that characterizes this condition is most obvious in the shoulder and pelvic girdle musculature,[23] but usually also affects the extremities. The tendon reflexes are usually diminished. Muscular fasciculations are occasionally present. The thyroid gland may be normal in size and consistency, or enlarged. The characteristic manifestations of hyperthyroidism may be present, but not infrequently they are so mild that the weakness is erroneously attributed to progressive muscular atrophy or to some other cause. The appearance of some of these patients has led to application of the term "apathetic hyperthyroidism". Treatment of the hyperthyroidism results in rapid improvement in strength and weight and correction of the muscular wasting.

Weakness of the extraocular muscles may occur in hyperthyroidism, often without any pronounced weakness elsewhere. This occurs in a

most severe form in exophthalmic ophthalmoplegia. This manifestation of hyperthyroidism is frequently unimproved by therapy and may get worse after thyroidectomy.

Hypothyroidism. Virtually all patients with hypothyroidism have some degree of weakness and fatigue. In contrast to patients with hyperthyroidism, however, the muscles are normal in bulk or occasionally have increased bulk and consistency. In addition, there is usually some muscular stiffness and slowness of movement, and occasionally muscle cramps, pain, and slowness of relaxation, which in rare instances may be so marked as to be suggestive of myotonia.[24] Treatment of the hypothyroidism results in relief of muscular symptoms.

Hypo- or Hyperfunction of the Adrenal Cortex or Anteroir Pituitary. Weakness is a prominent manifestation of hypoadrenalism (Addison's disease) and hypopituitarism (Simmond's disease, Fröhlich's disease) and may also occur in hyperfunction of the adrenal glands or pituitary gland (Cushing's disease, acromegaly). Severe weakness and wasting of the muscles of the pelvis and lower extremities may also occur after prolonged administration of large doses of 17-hydroxycorticosteroids, particularly triamcinolone and fluorocortisone.[25] There is increased creatinuria and minimal histologic change. Potassium administration does not affect the weakness or wasting, but discontinuation of steroid is followed by return to normal. Steroid myopathy is believed to be due to altered protein metabolism, but the mechanism is not clear.

Hypo- or Hyperparathyroidism. In hypoparathyroidism muscular weakness may occur in association with tetany and muscular rigidity due to diminution in the serum concentration of calcium. In hyperparathyroidism, muscular weakness, flaccidity and even wasting may occur, in association with increase in serum calcium concentration, diminution in serum phosphorus concentration and usually elevation in phosphatase activity.[26]

Myopathies of Unknown Etiology

Diseases of Mesenchymal Tissue: Varying degrees of muscle weakness and wasting, associated with round cell infiltration, perivascular collections of lymphocytes, and degeneration, necrosis and atrophy of muscle fibers, may occur in association with any of the mesenchymal diseases which have been attributed to hypersensitivity. The weakness

and wasting are least marked in acute rheumatic fever, more marked in rheumatoid arthritis and in some patients with disseminated lupus erythematosus, periarteritis nodosa or scleroderma, and most marked in dermatomyositis or myositis.

Dermatomyositis may begin at any age, with roughly equal distribution in all decades from the first to sixth.[27] The characteristic dermatitis usually begins in the face or upper trunk, with edema, erythema, and a pink "heliotrope" hue. The periorbital areas are particularly involved, and malar erythema may occur as in lupus erythematosus. The hands are frequently involved, especially the extensor surfaces and nailbeds. In approximately half the patients, the dermatitis precedes the weakness; in the others it accompanies or follows it. The histologic changes in the skin are not pathognomonic. Pigmentation, hardness and even calcinosis of the skin and subcutaneous tissues may occur as a late development. The muscle weakness is almost always proximal in location, affecting both shoulder and pelvic girdles, and in severe cases the muscles of swallowing and respiration may be affected. Muscle pain and tenderness, fever, weight loss, splenomegaly and arthralgia may or may not be present. The tendon reflexes tend to be diminished when the muscles of the extremities are involved. The muscle biopsy, if it includes an involved area, shows infiltration of mononuclear cells and usually evidence of muscle regenerative activity, in contrast to muscular dystrophy. The electromyogram may show evidence of increased irritability, including fibrillation potentials and "pseudomyotonic" discharges, which occur only rarely in dystrophy.[27] In approximately 10 per cent of adult patients there is an associated malignancy, usually carcinoma arising in the breast, rectum, colon, cervix, ovary or lung.

While some patients succumb to the disease within a few weeks, the great majority reach a peak of maximal severity in one to two years and continue to have residual disability, although occasionally complete recovery may occur. The active stage of the disease usually responds to large doses of adrenal steroid (30 to 50 mg. of prednisone daily), which are reduced after about a week to a maintenance dose. Steroid should be discontinued as soon as possible, although it may have to be readministered in case of recurrence of activity.

Polymyositis, which is probably the commonest primary myopathy, has the same characteristics as dermatomyositis, except for absence of dermatitis.[28] In many patients, systemic signs are absent, and the course

is so chronic that the picture may resemble muscular dystrophy.

Muscle Necrosis Associated with Myoglobulinuria. In this rare disease, which has been called paroxysmal paralytic myoglobulinuria, there are usually recurring attacks of muscle pain, tenderness and weakness, followed by darkening of the urine due to the excretion of myoglobulin from degenerating muscle fibers.[27] These episodes are usually transient, but occasionally the muscles of respiration may be affected, leading to respiratory paralysis. The myoglobulinuria usually does not cause renal impairment, but when very marked may result in tubular damage, anuria and renal failure, especially if hypotension occurs.

Muscular dystrophy. The dystrophies are degenerative and usually familial diseases of muscle with weakness and atrophy and without evidence of muscle regeneration, such as is seen in myositis. There are several types of dystrophy, including the severe, generalized, rapidly progressive type, the mild, restricted, slowly progressive fascioscapulohumeral type, and the intermediate limb-girdle type. Usually the muscles of the pelvic and shoulder girdles and the proximal muscles of the limbs are most affected. The initial manifestations, related to weakness of the pelvic girdle musculature, include the characteristic clumsy waddling gait, and difficulty getting up from a squat position and in climbing stairs. Weakness of the shoulder girdle results in difficulty in raising the arms, and winging of the scapulae. The tendon jerks of affected muscles are diminished or lost. Wasting, which may or may not be preceded by pseudohypertrophy, occurs and later there may be contractures. In less than 10 per cent of patients the heart is affected and congestive heart failure may occur. If the muscle biopsy includes an affected area, histologic changes include alterations of muscle fibers with varying degrees of fat deposition and connective tissue proliferation, and usually little or no leucocytic infiltration or evidence of regenerative activity. Occasionally the latter changes occur, and may make histologic differentiation from myositis difficult. Biochemical changes include increased urinary creatine excretion, probably due to decreased muscle mass and decreased conversion of creatine to creatinine, increased urinary pentose excretion and increased serum levels of aldolase, glutamic oxalacetic and pyruvic transaminases, lactic dehydrogenase and to a lesser extent phosphohexoisomerase, resulting from leakage of these enzymes out of muscle.[29]

The extraocular muscles are seldom involved in the above types of muscular dystrophy. There is, however, a less common type of dystrophy which affects the extraocular muscles; namely ocular myopathy, or progressive dystrophy of the external ocular muscles. This disease, which usually starts before the age of 20 but may begin at any age, involves the extraocular muscles initially, with ptosis nearly always the first sign.[30] Progression is slow, but the muscles that move the eyeballs are next affected and complete external ophthalmoplegia usually occurs sooner or later. Diplopia is sometimes an early symptom, but usually soon disappears owing to the slow and often symmetrical development of the ocular palsy. In most patients, the disease is limited to the extraocular muscles, but in 25 per cent the orbicularis oculi and other facial muscles are involved. In 10 per cent the muscles of mastication, neck, and limb girdles also become affected. The histologic changes in the eye muscles enable identification of the dystrophic process.

In the myotonic form of muscular dystrophy there is not only wasting and weakness, but also myotonia, and frequently frontal baldness, cataracts and evidence of testicular or ovarian atrophy. The muscular wasting is usually most marked in the facial muscles, sternomastoids, shoulder girdle and extremities. Ptosis may be present, and weakness of the pharyngeal muscles may result in a weak, nasal voice. The myotonia is manifested by slowness of muscle relaxation after voluntary contraction or after percussion with a reflex hammer. The latter is best seen in the muscles of the thenar eminence and in the tongue. The myotonia may be improved to some extent by the administration of 0.6 gm. of quinine sulfate every four to eight hours, but there is no treatment for the muscular weakness or wasting.

Summary

Weakness may result from emotional causes, disorders of the upper or lower motor neurone, or abnormalities of the neuromuscular junction or muscle. Some of the latter result from a known disturbance of the chemical environment, whether due to deficiency or excess. Deficiency in the action of ACh on the neuromuscular junction in myasthenia gravis can be detected and treated by the specific effect of anticholinesterase compound, while excessive action of ACh in anticholinesterase intoxication can be detected and treated by the effect of oxime. Weakness due to hypokalemia or hyperkalemia can be identified by

means of the serum potassium level and the electrocardiogram. Weakness due to hyper- or hypofunction of the thyroid or adrenal cortical glands can be diagnosed by tests of thyroid and adrenal function. After these disorders have been excluded, a muscle biopsy must be performed to detect those primary diseases of muscle for which there are, as yet, no known chemical or pharmacological changes of diagnostic value.

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EXISTENTIALISM AND PSYCHIATRY*

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IT is difficult to define precisely what existentialism is, not because existentialism is lacking in definable components, but because it is endowed with so many.

Existentialism has many substantive manifestations, in art, literature, philosophy, etc. But in and of itself existentialism is not "demonstrable". It is a dynamism, a social, cultural, and intellectual movement. As such, it can best be understood in its historic derivation.

Existentialism is primarily and essentially European but it needs must concern us deeply. Our interest in existentialism is not a pure exercise in intellectualism, but a wise attempt to anticipate what is bound to confront us in the not too remote future.

Europe and we are an ocean apart, but we are culturally contiguous. Between Europe and ourselves there is a time lag of some twenty years or so, in the emergence of historic and cultural issues and problems. It is therefore a safe assumption that what is culturally crucial to Europe today, will be crucial to us one generation hence. Existentialism agitates Europe today. It will stir us on the morrow. Even now one can perceive its prodromal signs in our midst.

What is existentialism? First and foremost it is a movement of protest. It is a challenge to, and a denial of, things past, of the philosophical, the theological, the psychological, the aesthetic, the moral, and, I need add, the scientific theories, dogmas, and assumptions of the past. It is, in the phrase of Nietzsche, an attempt to transvalue values—by initially denying the validity of existing values.

Existentialism is revolutionary and culturally discontinuous. Existentialism does not offer to modify classical thought—it denies its validity. In contrast to classical philosophy which tries to make life conform to thought, existentialism seeks to make thought conform to

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life. Existentialism reduces life from that what we would like it to be, to what it is.

The existentialist movement constitutes an unprecedented reorientation of human thought in that it denies existence to everything of which we are not immediately and indubitably aware.[1]

Existentialism is a challenge of colossal dimension and of transcending importance. Existentialism has engaged the interest, and has enlisted the intellectual, aesthetic, and creative energies of some of the most competent and earnest of men: poets, philosophers, playwrights, painters, novelists, theologians, psychologists, and psychiatrists.

Existentialism has its antagonists as well as its protagonists, and both are in earnest. Norberto Bobbio, Professor of Legal Philosophy at the University of Padua, and Editor of the *Rivista di Filosofia*, wrote a series of essays on existentialism, titling them *The Philosophy of Decadentism*. "Existentialism," he wrote, "is a mode of philosophizing which in a strange and wonderful way accords with the philosophical vocation and, I would say, the philosophic vogue of our time. As such, we harbor it with an easy conscience or defiantly, with pride or repugnance, and we harbored it as an aspiration or as a temptation even before it was revealed to us in specific terms." [2]

Bobbio recognizes that existentialism is a philosophy of crisis. He fails however to identify the true derivation of that crisis. He ascribes it to the disordered exuberance and unrestrained vitality that follows on the weakening of authority. By authority he intends "the supreme principles which inspire every manifestation of spiritual life both in the theoretical and in the practical spheres." [3] It were profitless to argue Bobbio's criticism of existentialism. However, we can accept his notations on "crisis" and "the weakening of authority."

Existentialism *is* a philosophy of crisis, and this being the case we needs must ask what is the derivation, and the nature of this crisis. Also, since the weakening of authority is both antecedent and consequent to crisis, we need to inquire what authority has been weakened.*

As the starting point I would take the years that witnessed the rise of the Modern Age and the birth of Modern Science—that is, the last decades of the sixteenth and the early years of the seventeenth century. These are the years of Galileo (1564-1642) and of Descartes (1596-

* Needless to say time will allow for no more than a hasty and, I fear, somewhat superficial treatment of these questions. Those who would study these matters more deeply will find José Ortega y Gasset's *Man and Crisis*, W. W. Norton & Co., N. Y. and Luis Diez del Corral's *The Rape of Europe*, Macmillan Co., 1959, most helpful and illuminating.

1660). This was the *new* era, emergent from Mediaevalism, and the Renaissance. This was the Age when mankind, aided and abetted by its scientists and determinist philosophers, took in earnest the exhorting counsel of Francis Bacon, to wrest from nature the secrets of its ways, so that man might master both nature and his own destiny.

No age had ever been ushered in so brilliantly, and with so much hope and expectation. No age had been welcomed with so much enthusiasm by those who were called, and who considered themselves to be "the enlightened".

It was not long, however, before both the hopes and the expectations of that nascent era were dimmed by frustrating reality. Life became not better, but worse. The common man suffered not only physical hardships and deprivations, but what was of greater evil, moral degradation, and a deep, inextricable confusion as to life's meanings and values. Emergent science implemented the industrial revolution, with its nasty slums, its disenfranchised proletariat, its ugly factories, and its gross inhumanities.

The Modern Age had hardly reached its adolescence when it was literally macerated by the bloody and disruptive French Revolution. Inspired as it was by so much of the heroic and the humane, this revolution, as revolutions are likely to, soon "got out of hand", monstrously consuming countless thousands of humans, including most of its own initiators. The French Revolution was even more disruptive than bloody. The French Revolution left in its heritage the miseries of Nationalism and of the Citizens' Army. The French Revolution made way for the man on horseback, for Napoleon, the ambitious and unscrupulous usurper. His breed has become all-too-well known to us in the passing decades. Titled as they are—Duce, Gauleiter, Caudillo, Fuehrer, or Comintern Secretary—they have taken it upon themselves to "carve out" the destinies of Europe in the patterns of their ambitions. They have brought misery and death to countless millions, and have sown dissension, suspicion, hatred, and blood feuds among the peoples. Yet they, the ambitious and the unscrupulous usurpers of power, are not the primal evil. They are secondary and consequent evils. The primal evil is of another and deeper nature.

The crisis of our age, as has been observed, is of a moral, of a spiritual nature. Ortega has phrased it well in affirming that "crisis occurs when the system of convictions belonging to a previous genera-

tion gives way to a vital state in which man remains without these convictions and, therefore, without a world."[4] It is the loss of convictions that engenders our world crisis, a crisis which is moral in nature, and hence more menacing.

The modern crisis was long in the making but precipitous in its emergence. It came to the fore with the First World War, and has become enlarged and intensified ever since. How well, and with what keen prescience, Viscount Grey summed up the tragic outbreak of the World War of 1914: "The lamps are going out all over Europe; we shall not see them lit again in our lifetime."

For more than three score years, that is, from the middle of the nineteenth century until 1914, Europe lived in the persuasion that it had attained basic stability and had mastered the means for a continuing melioration of mankind's lot. The means were obvious and simple, interrelated and mutually reinforcing. They were: education, industry, and democracy. They were means, but also innately good and rewarding in themselves. It was good to be educated; industry yielded the products essential to a good life; democracy extended the prerogatives and the responsibilities of government and enhanced the dignity of the individual.

These persuasions were bolstered by the moralisms and "sage saws", native and dear to the Victorians. There is, it was argued, a logic, a rationality, a [illegible] sense to life. If one played the game according to the rules, worked hard, stayed sober, saved his money, was decent, and otherwise did his duty by God, country and family, one was bound to prosper, and the world too, accordingly. The greater number of Europeans believed all this in earnest.

But then came the World War with its Armageddon aftermath. The conceits, the persuasions, and the faiths of the world, were now discredited by gaunt reality. Experience proved them hollow, false, corrupted, and corrupting, thus giving warrant for Sartre's later affirmation, "Human life begins on the far side of despair" (*The Flies*).

The newer generations of sensitive, inquisitive, thoughtful men, contemplating the ruin about them, denied the household gods of their fathers. But, they sought no new gods! They turned to other ways and other sources for the meaning of human life and of human experience. Their search and their labors came to fruition in existentialism.

I have said the crisis was long in the making, and that is correct.

There were, in effect, existentialists before existentialism came into being. There were some early "prophets of doom", a cletch of Cassandras, who foresaw and foretold the oncoming tragedies. They were a varied lot, including theologians, philosophers, poets, novelists, and artists. Kierkegaard was among them, and Nietzsche, Baudelaire, Stern, and Kafka. These early existentialists were the "odd men" of the Victorian era, those whom Max Nordau labelled the Degenerates.*

The global crash of 1914 heralded the emergence of the Crisis of our Age, and to this Crisis we can credit the materialization of Existentialism.

Existentialism is, as we have already noted, a movement of protest, and a philosophy of despair. These are its initial and elemental qualities. But existentialism is more than formalized protest and despair. It is creative far more than it is polemical.

Existentialism is not nihilism. It is, on the contrary, an energic, creative impulsion. It has animated and inspired the graphic arts, poetry, drama, and every form of prose literature. It has productively agitated and illumined the philosophers, the psychologists, and the theologians.

That is precisely why it is so difficult to "define" existentialism, save in terms of its historic derivations. For the problem is: whose existentialism is prototypical—Sartre's, Camus', Kafka's, Nietzsche's, Kierkegaard's, Jaspers', Heidegger's, Tillich's, or Martin Buber's? Existentialism, however, is not a babel of tongues, not a rat's nest of confusion that carries a delusionally unifying label. In Sartre, Camus, Kierkegaard, Buber, et al., the accents differ—but the tongue is common. It is that of existentialism.

The key factor in the comprehension of existentialism is existence. This affirmation seems tautological. All existing things—exist! But that is not the sense in which existentialism speaks of existence. For the existentialist existence is not, like endurance, a derivative state. Existence is dynamic, creative, emergent, mercurial—a flux of "being, becoming, and being". This affirmation is not novel nor entirely new. The Greek philosopher Heraclitus propounded a comparable version of living experience. Nothing remains what it is, everything passes into its opposite, all comes out of all; all is all. But where the Greek theory was formulated primarily to *describe* the flux of experience, the existentialist intends his version of existence initially as a protest against the philo-

* Even so sage and cosmopolitan a spirit as George Brandes found nothing in Kierkegaard that merited more than derision and dispraise.

sophical and moralistic systems which have arisen in time and which hedge existence with a host of logical formulations and moral injunctions. Secondarily, but in an even larger intent, existentialism affirms the sovereign creativity and "rationality" of pristine existence, of existence unencumbered by preconceptions as to what existence *ought* to be. The rationality of existence, the existentialist insists, is innate in existence and emerges in the existence of being and becoming. All of this is reflected in the existentialist affirmation that "Truth is not formulated but lived". "Classical philosophy considers existence a secondary phenomenon, an appearance behind which it should be possible to discover a rational order, invisible on the surface." [5] But the existentialist reverses the order and the emphasis: existence is primary and authentic,—thought and theory are secondary and derivative. The world and life do make sense, but not in the way orthodox philosophy, and doctrinaire moralities suppose they do. Certain it is that historically, and most notably during the past century, the orthodox philosophies and the doctrinaire moralities have been shown to have only the most tenuous relevance to experienced reality.

The emphasis here, be it noted, is on the *orthodox* philosophies, and the *doctrinaire* moralities. Existentialism does not deny the possibility of philosophy, or morality. But, the existentialist affirms that, to be authentic, philosophy and morality will need to be not *antecedent* and *a priori* to experience, but derivative from existence.

There is a good deal that is seemingly paradoxical and contradictory in the existentialist contentions as represented in the aforegoing. If existence is neither to be envisaged, nor governed by any antecedently formulated theories or preconcepts, but is conceived as purely self-emergent and auto-directive, then can existence in effect add up to anything more than a spiralling anarchy that must inevitably end in dissolution? Reading Sartre, one can perceive in the destinies of his principal characters just such spiralling anarchy that ends in dissolution.

"Sartre's man," wrote Norberto Bobbio, "is the sheer antithesis of the Christian God, who creates the world out of nothingness; he (Sartre) creates nothingness out of the world".[6] But that is Sartre's existentialism, predominantly protest in character. Other existentialists, notably the philosophers, psychologists, and the theologians, have gone beyond the protest phase and have concerned themselves with the ontological aspects of existence.

Confessedly, the ontological is the least well developed and the least well defined component of existentialism. Yet it is crucial to, indeed the very complement of, existentialism. For it is its ontological perimeter, framing the miscellany of existential critique, psychology, and philosophy, that renders the existentialist entirety meaningful and comprehensible.

The term ontology is commonplace in existentialist vernacular. Sartre's *L'Etre et le Néant* carries the subtitle *Essai d'ontologie phénoménologique*. Existentialism itself is not infrequently referred to as an ontological philosophy. However, ontology in existential expositions most commonly refers to the operational modality of existence: to the *becoming* phase of existential being.

In existential psychology, as expounded by Heidegger, being is of two orders, *being* with the small "b," and being that is written and understood with the capital "B." The initial being, that of the small "b," emerges out of nothingness, and sequentially yields to nothingness, which, in turn, yields being of the small "b." The whole experimental process adds up, in the perspective of extended existence, to *being* with the capital "B." This cyclical process involving the sequential flow of nothingness into being, and being into nothingness *is* the ontological dimension of existence.

All this is confessedly an uncommon formulation, and difficult, at first, to comprehend. It will help to understand that by nothingness the existentialist intends not insubstantiality but an irrelevant state, that is one that is not pertinent to any immediacy: like "yesterday's snow."

Existential psychology strongly emphasizes the certainty and the authenticity of the experienced moment, in the here and the now. This existential moment is forged into being out of the antecedent nothingness. The existential moment in turn will yield to nothingness, from which the succeeding authentic existential moment will emerge.

This formulation displaces and discredits the Cartesian *cogito ergo sum*–I think, therefore I am–and affirms instead "I am what I am," or "I am as I am", or "I am because I am". This, in effect, is a paraphrase of Jahve's answer to Moses. When Moses, in the presence of the Burning Bush asked God (Jahve) what is his name, God answered Moses: "I am that I am".

There is something appealing in the affirmation of the authenticity

of "being in the here and the now." It is so patently real, so immediate and so undeniable. And yet it is also so very inadequate. For the here and the now brings with it the echo of the "there and then" of the "here and the now *that was*," and that now is melted into the nothingness of the past, that no longer has an immediacy, save in the residual pattern of individual antecedent, and collective history. The "here and the now" is authentic and immediate, but it is also impermanent, fugitive, and evanescent.

Contemplated in the larger perspective, the existential moment is seen as the link between past and future. The existential moment of the *here* and the *now* is bounden to, and gives issue to the *there* and *thereafter*. In this sense then, the existential moment is ontological. But it affirms only the ontology of the operational modality of existence. It is initial but not amply definitive. It relates to process, not to end result.

It must be said that if existentialism did no more than propound the *operational* ontology of existence, it would already have done a great deal; for modern science has shied away from ontology: ontology smacks too much of vitalism.

The philosophic and the theological existentialist–among the latter we may count Paul Tillich, Martin Buber, Jacques Maritain, and Nicholas Berdyaev* are not, however, content to rest with an operational ontology of existence, one that is merely concerned with the *process* of being; they reach beyond, to the ontology of the total experience of being, of being with the capital "B". Existence, they argue, cannot be the ultimate rationale of existence. All human experience controverts that postulate. There is, they insist, a perceptible pattern to human life, a pattern which emerges from the immediacies of sequential existence. This pattern is not accidental to existence, but rather attests to the significance of extended existence pattern indwelling, but not manifest, in the singular existential moment. This pattern is the ontology of *being*, with the capital "B".

The philosophic and theological existentialists are not thus attempting to sneak in, under the cloak of existentialism, the old and familiar ontology of predetermination. They most earnestly subscribe to the existentialist faith that "the visage of the world was not preordained, that man is free to mold one that suits him, and to abandon it as soon

* Will Herberg, *Four Existentialist Theologians*, Doubleday & Co., N. Y., 1958.

as it ceases to suit him".[7]

It is here that we come plumb of the relevance of existentialism to psychiatry. The metaphysics of existentialism and its psychological *aperçus* may interest the psychiatrist as a man of this age, himself involved in its cultural crisis. The ontological concepts of existentialism, however, deeply relate to the *métier* of the psychiatrist, and involve his professional operations.

Let me state the arguments bluntly. All problems that properly fall within the psychiatrist's ambient are ultimately existential in character, and ontological in nature. The psychiatrist is called on to treat the individual who is experiencing an existential thwart, whose being and existence encounter frustration and negation, who cannot, in other words, get on with the flux of his existence, and is thus hampered in effecting his unique ontologic fulfilment. To continue in this metaphoric mood it may be said that classical psychiatry, including psychoanalysis, is primarily and almost exclusively concerned with "what blocks or diverts the individual"; existential psychiatry, on the other hand, is concerned with what blocks the individual from getting *on to where*.*

The extension of concern from "what blocks the individual" to "what blocks him from getting where," is of crucial significance. Failure to comprehend this is responsible for the frequency of that cynical comment: "His analysis was successful, but he himself is no better." The "where" of the psychiatric problem is not to be determined by an *a priori* judgment, nor in accordance with some pattern or schedule of normalcy. It can be grasped only by an intimate study of the existential history of the individual, and this is more than his anamnesis, or the produce of his free association. Reference to free association raises the question of the relation of psychoanalysis to existential psychiatry.

Freud was no existentialist, though he had a profound regard for Nietzsche's psychological insights. But Freud was something of an existentialist, at least in his recognition of the extent to which modern man is alienated from his primal self, from that which is Nature in Man. Freud regarded both nature and culture as twin millstones that grind the marrow of man's being and render his life bitter and a trial. But that despite, Freud was a 19th Century man, and shared in that

* I must hasten to add that I cannot really conceive of an existential psychiatry, *sui generi*, though I can appreciate how much psychiatry stands to gain by the incorporation of existential insight.

Century's faith in the ultimate competence of Science to render man free, prosperous, and happy.

That was Freud's belief, his faith, and many shared it with him; but with time and experience, some grew disillusioned. Freud and psychoanalysis, they found, were not enough, not adequate, to illuminate the psychological problems of modern man. Freud's orientation to man as a being, his formulations on etiology, pathology, and therapy in psychic illness, were remote to the living, unique, individual. They were abstractions, or extractions, stereotypic, projective formulations based on the concept of a generic man.

This is perhaps best reflected in Freud's doctrine on the passivity, remoteness, non-participating role of the analyst; in Freud's unique therapeutic procedure that of "free association"; and also most tellingly in the many "universals" which he enunciated, such as the Oedipus conflict, the castration fear, the pan-psychism of sexuality.

It was against this dismemberment of man, the remoteness thereby engendered, the falsity of absolute universals, the resultant alienation, the non-participating, non-committed role of the psychotherapist and of psychotherapy, that some among Freud's followers, Ferenczi, Sullivan, Horney, Frieda Fromm-Reichmann, protested.

Among the so-called existential psychiatrists there are many who, if not avowed psychoanalysts, are well informed on, and basically appreciative of, Freud's historic stature and his epochal contributions to psychiatry. Existential psychiatry is not avowedly anti-Freudian nor anti-analysis, but only critical of its limitations. The existentialist emphasis is on the uniqueness of the individual and of his existence, his being. Their protest is against viewing man, the patient, as a stereotypical individual, involved in a psychopathy, to be dealt with "stereotypically." What does this mean? Some insight into its meaning can be gained from Binswanger's concept of man as confronting a triple world in which he lives, and to which he must relate. This triple world Binswanger describes as the *Umwelt* (the world around), *the Mitwelt* (the with-world), and the *Eigenwelt* (the own world).

In existential formulation these three "modes of world" are always interrelated, and always condition each other. Man lives in the *Umwelt*, *Mitwelt*, and *Eigenwelt* simultaneously. It is Binswanger's contention, shared by many of the existential psychiatrists, that classical pyschoanalysis is preoccupied primarily, if not exclusively, with the *Umwelt*.

In Freudian terms the *Umwelt* would be the reality with which the patient is required to deal "realistically."

Existential psychiatry accents the need of the individual to relate effectively to each of the components of his tri-modal world. The existential psychiatrist maintains that excessive preoccupation with any one of the world modalities, to the exclusion of the other two, is both a product and an attestation of disease.

Perhaps the most important, though rather recondite element of this formulation is the following: the *Eigenwelt* is not simply a derivative or product of the *Umwelt* and the *Mitwelt*, but rather exercises a shaping influence on the *Umwelt* and *Mitwelt*, which then reflexly operates on the *Eigenwelt;* or to paraphrase this at a simpler level, individuality is not a derivative product of nature and nurture, but itself contributes to the interplay of nature and nurture, and is thus a catalytic morphogenic factor.

This is the accent identified in existential psychiatry as the "ontology of existence". It is here that we can perceive the distinctive orientation of *existential analysis*. In existential analysis the "analyst" seeks to understand, not judgment-wise, but in simple comprehension, how the individual is dealing with his tri-modal existence in his tri-modal world. The "phenomena of his operations", what we might in psychiatry call his psychodynamic pattern, and in the case of the ill person, his psychopathology, thus represent a meaningful understandable operation. Pathology is thus perceived as a mode of relational operation. The existential analyst does not condone or condemn but merely understands.

Binswanger has described the existential analysis of a case under the title "The Case of Ellen West". It makes most interesting and, I must confess, rather disturbing reading. It is strictly a "phenomenological portrait". There is nothing in "The Case of Ellen West" that can warm the heart of the psychiatrist. There is nothing in it of the familiar depth psychoanalysis. We find nowhere any evidence of participation or intercession by the therapist. This case recitation reflects, in truth, a contemplation of the slow ingression and the ultimate triumph of death.

Yet the case recitation, chilling in its over-all perspective, is instructive in its own, peculiar way. There is a good deal in it that the analytically oriented psychiatrist can absorb and utilize in the deeper and larger comprehension of his patients.

I have underscored the fact that existential analysis, at least insofar as it is represented in Binswanger, offers little illumination on what the existential analyst *does* or, to paraphrase it, what the *technique* of the existential analyst is, and how it differs from the techniques of other psychiatric practices.

Rollo May, in his book *Existence*, emphatically affirms that existential analysis offers no novel therapeutic techniques. "The fundamental contribution of existential therapy", he writes, "is its understanding of man as *being*. It does not deny the validity of dynamism and the study of specific behavior patterns in their rightful places. But it holds that drives or dynamisms, by whatever name one calls them, can be understood only in context of the structure of the existence of the person we are dealing with. The distinctive character of existential analysis is, thus, that it is concerned with *ontology*, the science of being, and with *Dasein*, the existence of this particular being sitting opposite the psychotherapist." [8]

Referring to Binswanger's *Daseinsanalyse*, that is, existential analysis, Rollo May states: "What Binswanger termed Daseinsanalyse (Existential Analysis) represents a synthesis of psychoanalysis, phenomenology, the existentialist concepts modified by original new insights. It is a reconstruction of the inner world of experience of psychiatric patients with the help of a conceptual framework inspired by Heidegger's studies on the structure of human existence".[9]

There is in all this a great profundity and a something which is deeply appealing. And yet, to those who have wrestled with the problems of existence, Existentialism appears incomplete and hence inadequate.

Existentialism conceives of man as a sort of monadic being, floating in a realm of total indifference. It fails to take into consideration *man as a creature with an existential history*. It fails to recognize man as a *social* and hence a cultural being. The individual *emerging* out of nothingness into existence is inevitably confronted by a variety of alternatives. He is confronted with the necessity of selecting one from among the many alternatives. *That* choice is influenced by antecedent existence and by anticipatory evocatives.

To paraphrase this: man realizes his existence in the interplay of the dynamics of his past with those of his future.

I must end with one pertinent observation. Taking a closer view

of existentialism one finds that what originally seemed strange and alien begins to sound somewhat familiar. We discover like Molière's *Bourgeois Gentilhomme*, that we have been, at least in some measure, thinking and acting existentially. Such indeed is the case, yet I submit that it is not quite enough. It is not enough merely to "appreciate Existentialism by non-intention". The existentialist movement, existentialist philosophy, existentialist analysis, confronts us as a deep challenge which we need to comprehend clearly and definitely.

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CHANGING VIEWPOINTS IN MEDICAL PROGRESS*

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I FELT very much honored by the invitation of your Chairman several weeks ago to address you this evening. It has been a real pleasure as well as an honor to come to New York and to see at first hand the many-sided educational program which The New York Academy of Medicine sponsors. I am getting old enough now to be allowed to reminisce a little. I can recall my first visit to this Academy as a medical student when I came here to say hello to one of my greatly admired friends, who was the librarian, Dr. Archibald Malloch. He introduced me to the then current President, Dr. Samuel Lambert, whose colorful verbal reactions to whatever we talked about greatly interested and entertained me. Since then I have had the pleasure of coming to know Dr. McLeod Riggins, particularly in the American Clinical and Climatological Association, and of serving as a fellow-officer in that Association with your most recent past President, Dr. Robert Levy. Finally, I must mention how well and how happily I recall the advent some 30-odd years ago of a fellow house-officer at the Peter Bent Brigham Hospital, Dr. Frank Glenn, your current President. And so, I feel here very much among friends.

I think it only fair, when one has chosen as obscure a title as I have this evening, "Changing Viewpoints in Medical Progress", that some explanation for the choice should be offered. This I shall attempt to give you. A few months ago it became my privilege and duty to address a medical group in the capacity of presiding officer. I pondered at considerable length as to how this might be accomplished. To one who greatly prefers to avoid dissent, who abhors abstraction and is skeptical of nearly all prophets, the assignment seemed almost unconquerable. I felt like Meredith Willson trying to write *The Music Man*.[1] Willson

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describes how, for three years, he stared at four words atop a blank piece of paper; ACT ONE, SCENE ONE. There they were "committing you, in some horrible way, like your name was Faust and you just signed a contract with the Devil".

To be sure, an abundance of medical problems came to mind, all of them ripe for discussion, but nearly all of them depressing and rather gloomy, utterly unlike the atmosphere and the tenor of the association I was addressing. Glance momentarily down the list:

1. Free medical care for the elderly, a recognized forerunner of Socialized Medicine.
2. Our expanding population and with it the need for more doctors, for more medical schools, and, therefore, the need for lots more money, and where is that to come from? And if the percentage of grade A applicants to our medical schools falls off much more, where are we to find our future doctors?
3. The changing patterns in our highly respected profession which clearly have robbed it of some measure of public esteem. This unquestionably is due in part to lack of compassion in the makeup of a good many doctors. The trend has even led some to ask, "Is medicine still a profession or has it become a business?" Just where should "medical management" and other third persons in medicine fit into *our* scheme of things?

These and comparable topics all troubled me. And then, on one occasion, while meditating on some of the pleasant phases of my task, there came the awareness of what a transformation of thinking had encompassed my own brief medical career. Here I was, 35 years ago, an intern in an era when to get married during one's internship was seriously frowned upon, if not forbidden. Now the unmarried intern is the exception rather than the rule, and, in 1960, here I was about to officiate in a medical society in which *one* endorsement for membership was a charming and attractive wife. What progress in social thinking! What an evolution in a point of view! This idea of how our viewpoint changes with the passing of the years has for a long time interested and even fascinated me. All of us can remember that very steep hill or enormous green pasture of our childhood that became, after some years, only a gentle slope or a modest meadow. We can all recall, how as college freshmen, we looked on the 35-year reunion class as a bunch of old duffers, only to find that at our own 35th reunion we were still, after

all, a pretty young bunch and, indeed, how very youthful and immature the freshmen had become! A certain amount of all of this is just a matter of growing up, but there is more to it than that. The evolution of one's point of view in medical thinking is interesting to analyze. How much it changes and *must* change every year if progress is to continue as a part of our life! We may well ask ourselves, how nimble are we, individually or collectively, in changing our viewpoint when new ideas come along?

Without attempting the role of historian, I want to call to mind several advances in our medical knowledge during the past 50 years and comment on the change of thinking that each of them brought about. I do this with no sense of criticism but to emphasize what is sometimes required to change our point of view.

In 1912, not quite 50 years ago, there was read before the Association of American Physicians a paper entitled "Certain Clinical Features of Sudden Obstruction of the Coronary Arteries" by Dr. James B. Herrick of Chicago.[2] In this paper, Herrick makes clear how often coronary occlusion had been recognized even before 1912, both by clinicians and by pathologists. He mentions the writings of Cohnheim, Krehl, Dock, Osler, Obratzow and Straschesko, and others. In 1912, however, coronary occlusion was thought to be an almost invariably fatal event. Herrick's description of the clinical features of coronary thrombosis makes fascinating reading even now, nearly 50 years later. I would like to read to you several paragraphs of his paper:

> "A study of cases of this type shows that nearly all are in men past the middle period of life. Previous attacks of angina have generally been experienced, though as shown by my first case, the fatal thrombosis may bring on the first seizure. The seizure is described by patients who have had previous experience with angina as of unusual severity and the pain persists much longer. In some instances there has been no definite radiation of the pain, as to the neck or left arm, though this may have been a feature of other anginal attacks, and the pain, as in these two cases, may be referred to the lower sternal region or definitely to the upper abdomen. Cases with little or no pain have been described."

> "Dyspnea and cyanosis have been variable at times, much less than one would expect from the character of the accident and the quality of the heart's action. Rales, dry and moist, have been present in many cases, in some as in my first case, largely moist, diffuse, not very large. Here there was a moderate

amount of thin, frothy, slightly blood-tinged fluid expectorated, as in edema of the lungs, which condition was found at the autopsy."

"The weakness of the heart and the low blood pressure will account for the scanty urine and the trace of albumin. A palpable liver may likewise owe its enlargement to passive congestion.

"Nearly always the mind is clear, at times unusually clear, until toward the last. Some patients seem conscious, as is so common with angina, that they are face to face with death, but in none that I have seen has there been uncontrollable fear or the restlessness of fright. The seriousness of the accident seemed to be realized, but there was no panic. Perhaps the relief from the agony of the initial pain causes an unnatural mental calmness.

"General weakness has been marked in some cases, in others not. One patient showed for more than a week an asthenia comparable to that of the terminal stage of pernicious anemia or Addison's disease."

"The occurrence of a serofibrinous exudate over the area of myocardial softening, with roughening of the pericardium, has been noted in several instances. This may explain a later precordial distress.

"Emphasis ought to be laid on the resemblance of some of these cases to surgical accidents. The sudden onset of pain over the lower sternal and epigastric region, the nausea and vomiting, the tympany, the feeble pulse, ashy color, cold sweat, and other signs of collapse make one think of such conditions as gall-bladder disease, acute hemorrhagic pancreatitis, perforation of gastric or duodenal ulcer, hemorrhage into the suprarenal capsule, etc.".

I have quoted Herrick's paper at some length to point out that what he sought to emphasize was that coronary thrombosis was not "merely a pathologic curiosity but in reality a clinical entity" which could be recognized ante-mortem and from which patients might recover. As Herrick later expressed it, the paper when read before the Association "fell like a dud". Only one member, Emmanuel Libman, discussed it, emphasizing the peculiar color of the skin of patients who survived attacks, and pointing out the importance of pericarditis as a complication which Libman implied might be the cause of the fever "which sometimes comes on after attacks of angina pectoris".

Herrick's paper failed to catch on anywhere just as had the reports of Dock, Osler, the Russians and others, and during the next six years he did a lot of what he called missionary work, writing and speaking about coronary thrombosis. This included two papers in the *Journal of the American Medical Association*[3] and another report read before the

Association of American Physicians in 1918.[4] So zealously did he himself believe in and preach the recognition of acute coronary obstruction as a clinical entity, that he even began to question his own "overenthusiasm" and to ask his colleagues if he "was becoming nutty". They thought not.[5] He found it hard to understand the slowness with which the medical profession's point of view had to change before accepting *his* point of view. "A few", he said, "listened attentively, more incredulously, the majority, indifferently."

It was nearly eight years before many others began to recognize the importance of this diagnosis. Even as late as 1920, American textbooks of medicine gave only passing mention to coronary thrombosis, speaking of it chiefly as a pathologic curiosity and a frequent cause of sudden death in medico-legal cases. In the early 1920's, a dozen or more papers appeared in the American literature and the horizon was widening. But the change in point of view came slowly and one may wonder, in retrospect, why it took so long. In 1926, Dr. Louis Hamman gave what I think is perhaps the best answer.[6] Writing on "The Symptoms of Coronary Occlusion", and expressing surprise that even in 1925 one could find no comprehensive and systematic account of these symptoms in textbooks, systems of medicine, or monographs on heart disease, he says the following: "The reason for this omission must reside in some peculiar way of *viewing the matter*, and this peculiarity, I believe, is no other than the complete mental fusion that has existed between coronary disease and angina pectoris. Coronary occlusion has been considered an episode in the progress of angina pectoris, a harrowing episode it is true, and yet but the dramatic ending of an interesting and varied clinical story. Medical authors long neglected to place it in bold relief as an independent clinical condition and therefore failed to note carefully and in detail all of its characteristic features and to draw so clear and definite a picture that any physician familiar with its outlines might recognize it almost at a glance. All of the older observations on coronary occlusion are buried beneath discussions of angina pectoris."

This was also Herrick's contention, and in his memoirs he notes that, had he, instead of looking for references under " 'coronary artery'. . . grasped the bibliographic significance of 'infarct of the myocardium' ", he would have unearthed much pertinent material that had been published prior to 1912.[5]

Such, then, was the transition in thinking concerning a condition

which has now become one of the leading causes of disability and death in the American public.

In contrast with this very slow acceptance of a new medical point of view, let us look at what happened when insulin first hit the front page in 1922. The first publication about insulin appeared in the *Journal of Laboratory and Clinical Medicine* of February of that year.[7] Three months later, Banting, Best, MacLeod and others presented, again before the Association of American Physicians, their paper entitled, "The Effect Produced On Diabetes by Extracts of Pancreas".[8] Here was an achievement for which the world had been waiting. It was immediately hailed as a boon to mankind. The discussion of the paper before the Association is interesting to review. Dr. Solis-Cohen said, "Let me voice my admiration for this extremely valuable and in many respects remarkable study." Dr. Rolin Woodyatt immediately recognized the work as marking the beginning of a new phase in the study and treatment of diabetes. "It would be difficult", he said in his discussion, "to overestimate the ultimate significance of such a step", and he moved that the Association tender to Dr. MacLeod and associates a rising vote expressing its appreciation of their achievement. Dr. Frederick Allen, referring to the work as almost miraculous, stated that the Toronto workers, "having a secretion free of toxic material hold unquestionable priority for one of the greatest achievements of modern medicine".

Everyone in the field of diabetes apparently went promptly to work on insulin, and a year later, in 1923, at the meeting of the Association of American Physicians, under the Presidency, indeed, of Dr. James B. Herrick, there were six papers on diabetes and insulin which took up the greater part of one afternoon.[9]

Here, then, the change in the point of view came about easily, quickly and with much less than usual frustration. So it was also when, in 1926, the use of liver in the treatment of pernicious anemia came promptly to life as an unquestioned advance in our medical equipment and thinking.

The fourth, and by far the most dramatic story of the evolution of a viewpoint of which I shall speak, concerns the discovery of penicillin. This saga has been most beautifully narrated by André Maurois in his classic biography of Sir Alexander Fleming, a volume that no one should miss reading.[10] The application of penicillin to our discussion concerning one's viewpoint is to be found in the character of Fleming

himself—a quiet, determined, incisive Scot who for years had sought in his laboratory to find an agent that would kill bacteria without destroying human tissues. This was his dedicated aim, despite the opposing attitude of his own chief, Sir Almoth Wright, who felt that immunization by vaccination was the only really good means of boosting nature's defenses.

Everyone knows the now famous legend of how, in 1928, Fleming discovered that a stray mould which had contaminated a culture in his laboratory had, by so doing, destroyed the colonies of staphylococci adjacent to it. One can imagine what may have gone through his mind as he reportedly remarked, "That's funny". The phenomenon of antibiosis had been recognized years before but never quite in this form. For Fleming this was, of course, no chance discovery; here was *exactly* what his prepared mind had been looking for. There followed, in fairly quick succession, the proof that the substance producing death of bacteria came from the mould *penicillium notatum*, that this substance was effective in very dilute solution, that it was nontoxic to animals, but also that it was devastatingly unstable, defying success in any of the then known methods of purification. Much of this is reported in Fleming's first paper entitled, "On the Antibacterial Action of Cultures of a Penicillium, with Special Reference to their Use in the Isolation of B. Influenzae." [11] In an introductory paragraph he states, ". . . . to avoid the repetition of the rather cumbersome phrase 'Mould broth filtrate', the name 'penicillin' will be used". This paper, described by Maurois as "a triumph of clarity, sobriety, and precision", appeared in 1929. The date is important in the light of what follows. When Fleming presented the substance of this paper in person to a Medical Research Club, it is reported that *it* fell like a dud, as had Herrick's first paper. During the period of discussion which Fleming hoped would follow *no one* asked any questions. He was reported to have remembered years later "that frightful moment" of silence which followed the reading of this first paper.

Time will allow us to deal only briefly with the events that followed before the full significance of this great discovery burst upon the world 11 and 12 years later. During this discouraging decade Fleming seldom doubted that he had the answer to his dreams; but he admitted that he could not get anyone interested in penicillin nor find a chemist who could extract it. Several groups of men expert in chemistry tried to

extract and purify it, but all met up with its baffling instability. Then, in 1935, came the amazingly effective sulfanilamide and its successors. Fleming accepted these drugs but insisted that he had something better. In 1936, at an International Congress of Microbiology, he demonstrated on agar plates the effectiveness of penicillin, but no one appeared to take any notice. In 1939, at a similar congress in America, he was pleased to find that a few workers, among them Dubos, knew about his penicillin but none had yet found the means of purifying it.

The breakthrough had its beginnings that year, 1939, when Florey and Chain, working independently at Oxford, though on a strain of Fleming's penicillium mould, found one secret of purification in freeze-drying or lyophilization. Here was a newer method that would allow for both removal of impurities and stabilization of potency. The crucial test in animals came in July 1940, just 11 years after Fleming had first named his mould juice "penicillin". Fifty mice were inoculated with a lethal dose of virulent streptococci. Twenty-five were treated with penicillin. Twenty-four survived. All of the 25 untreated animals were dead within 16 hours. The first test on human beings came nine months later in February, 1941. So startling were the results that there could now be no question about the real effectiveness of this "magic bullet". The evolution of the viewpoint which Fleming had championed for more than a decade now came about easily. Production and clinical testing became the big problem. How this, in turn, was mastered through Florey's mission to this country and through the ingenuity of American science, technology and industry is one of the fascinating chapters in medical history.

One could continue almost endlessly this retrospective account of how our viewpoint changes with progress. One could mention, for instance, the time that it took to change our point of view regarding the climatic treatment of tuberculosis. One could certainly mention the growth of Basic Science in modern medicine: of how hemoglobin is no longer just hemoglobin, and plasma globulin has grown into what has been called a whole "little world of giant globulins"; and how catarrhal jaundice, as it used to be called, is no longer thought due to a mucous plug in the ampulla of Vater but to a virus that affects the entire liver structure. The instances are many, and sometimes the whole cycle works in reverse so that a viewpoint evolved by too uncritical or too rapid a method of thinking has to be undone or completely reversed.

There is no simple solution to whatever problem this subject may present. No individual or group of individuals can have the omniscience or flexibility of mind that will recognize promptly all significant announcements or discoveries, and papers like Herrick's and Fleming's will continue at times to "fall like a dud". Others, like Banting's and Minot's, will be immediately accepted. The most lasting changes in our point of view will generally come slowly. Just as a child grows to manhood, which takes years to accomplish, so must much of our thinking evolve slowly and critically, molded by experience and an intelligent skepticism. Whether we are liberal in our viewpoint and change readily, or conservative and change slowly, matters not. The important thing is that everyone should have an open mind.

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MEDICAL ASSISTANCE FOR THE AGED*

REPORT BY THE

COMMITTEE ON PUBLIC HEALTH

THE NEW YORK ACADEMY OF MEDICINE

WHILE a medical program for the needy aged of New York State was in the discussional stage in the 1961 State Legislature, The New York Academy of Medicine was concerned about the practicalities of its effectuation. Now that the program is law, it is more urgently concerned.

The Academy's interest, it should be said at once, is actuated solely by its desire that the program succeed. Its views are intended to be constructive, not obstructive. Specifically, its interest centers upon the quality and quantity of medical care that will be provided to the beneficiaries. Both the criterion and the goal should be, the Academy believes, medical care that is satisfactory in quality and sufficient in quantity, but without excess.

This program has the potentiality of becoming ultimately, if not immediately, a large-scale operation. For, the elderly not only constitute an increasing proportion of the population, but also require more medical care and hospitalization than any other age group. To add difficulty to the need, there is discrimination against the elderly in prepayment insurance plans. It is fair to assume that the needy aged reflect these characteristics of the whole group, perhaps even to a somewhat greater extent.

In carrying out the program there are administrative duties such as determining eligibility, accounting and disbursing. But these should be incidental to the real purpose of the law, to provide medical care for the needy aged. For that purpose physicians are the key personnel. Under the law the program operates at two levels, state and local. The department in which authority and responsibility are vested at the state level determines the department controlling the program at the local level. In New York State this is the Department of Social Welfare. But in the final analysis it is the private practitioner at the local level who actually renders the service.

Several potential difficulties may be foreseen in effectuating a program of medical care for the needy aged with an eligibility clause. These difficulties are not fancies or speculations about highly improbable eventualities. They are realities that have already occurred, some with considerable frequency. One is the cost of

* Approved by Frank Glenn, M.D., President, The New York Academy of Medicine, May 10, 1961. Approved by the Executive Committee of the Committee on Public Health, The New York Academy of Medicine, May 8, 1961.

determining eligibility. Ordinarily the Academy does not issue opinions on apparently nonmedical matters, but eligibility for medical care and its determination can exert a profound effect on the amount and quality of medical service that is actually provided. When the cost for determination of eligibility runs so high that it consumes a disproportionate amount of funds appropriated for medical care, it becomes a grave matter. Determination of eligibility then defeats not only its purpose but also the major objective of the program, medical care of the needy aged. It raises the question of administrative efficiency in determining eligibility, or even of the wisdom of an eligibility provision.

The second difficulty is the overuse of medical service and hospitalization. When benefits are available on a mass scale, they are usually abused to a varying degree. Under all the circumstances of modern culture it is easy to rationalize a decision for admission to or prolonged stay in a hospital or nursing home. Tremendous pressure toward that end is a powerfully conducing influence. But overuse of benefits may reach the point of producing a deficit, which can be of a magnitude that in effect means a financial crisis. Overuse of hospitalization is probably the most troublesome problem in a medical benefit plan and it is difficult to control.

Equally disturbing but entirely different is the third problem arising in a medical care plan. It is the difficulty of a defect: inferior quality of medical care. The impression prevails that something may happen to the quality of medical service in the process of providing it on a mass scale. When the ingredients of indigency and governmental bounty are added, the result is not improved. Undoubtedly in some sections of the state the medical care of welfare recipients is satisfactory. But in the opinion of some experts, welfare recipients on the whole receive the poorest quality of medical care of any group. Yet it is not their indigency *per se* that is primarily responsible for their receiving medical care of lower quality. In the days when almost all the sick poor received their medical services free in the outpatient departments, they had care of highest quality.

After searching for the reasons for abuse of medical care plans and the questionable quality of their service, the Academy has reached the conclusion that the answer is sweeping and complex, not small and simple. Essentially it lies in the *modus operandi*. If a mass medical care program is to succeed it must have these provisions: 1) a unit controlled, directed and operated by professionals trained in medicine; 2) authority commensurate with responsibility; 3) organization and system; 4) standards and regulations governing the quantity and quality of medical care; 5) supervision to ensure adherence to standards and regulations. Too frequently in governmental programs these specifications are not met.

When a medical care program is entrusted to a governmental nonmedical department, it is apt to become a subordinate or side operation. Furthermore, such a department is not equipped by training to manage and direct it. It is not enough that the parent body place one or two physicians on its board, or appoint a medical advisory or consultative board, or hire a medical director alone or engage private practitioners by contract, or even turn over the actual rendering of services to a health insurance group. All this is a skeletal arrangement giving the semblance

of substance. Actually the parent department retains the authority and funds; it buys and delegates performance of service. The physicians who in reality render the service have the ultimate responsibility without real authority. For, the hand that controls the funds holds the power and authority. If such a program fails, all parties share in the blame, especially the physicians,—not just the participating physicians but the entire profession.

What department administers the program in New York State may well determine whether the goal of satisfactory medical care without abuses is achieved. Neither by logic nor by the record is the Department of Social Welfare the most appropriate unit to entrust with a program of medical care for the needy elderly.

The Academy is familiar with the argument that mainly the program presents an administrative task, so far as government is concerned, and that it is natural to have a welfare unit, that is already attending to the other needs of the indigent and marginal, take on the additional responsibility of providing medical care. By this line of reasoning it is evident that determining eligibility, accounting and disbursing are conceived to be the major and important part of the program, while provision of medical care is regarded as secondary. Such thinking surely contributes to the less than spectacular record of medical programs managed by welfare units. For, a medical need on a mass scale is a specialized need requiring specialized administration with autonomy, organization and professional knowledge. Neither at the state nor at the local level does the Department of Social Welfare meet these requirements.

In fact, the record does not inspire confidence or give promise that the funds will achieve their purpose of providing medical care of high quality with prevention of overuse. A recent survey of the Department of Social Welfare of New York State revealed that the cost of administering public welfare in the state is the highest on a case-month basis in the United States. This high cost does not arise from the state level but from local departmental administration. Most of it is the result of determining eligibility; relatively little is spent for social or rehabilitative services. Indeed, the basic orientation of the department was found to be toward determining eligibility and making prompt payments.

Furthermore, among the organizational weaknesses noted in the survey, two affect the administration of medical care: 1) A division of authority, responsibilities, and duties between the state and local governments prevents either level from making changes for improvement. This division is said to result in "high-cost and ineffective administration". 2) In medical affairs, the organizational pattern is further complicated in that the responsibility for medical care policy and program development and administration at the State level is shared by two units.

The Deputy Commissioner for Medical Affairs is a physician. In a staff capacity, his responsibilities are to advise the Board of Social Welfare and the administrative staff within the Department on policies and programs for medical care and health matters; and to evaluate and initiate changes in such policies and programs. In addition, he represents the Department as liaison officer in dealings with professional and related groups.

The Deputy Commissioner for Welfare and Medical Care, on the other hand, has no medical training. In a line capacity through the Bureau and Sections on Medical Care, his duties are: to develop policies, standards and procedures for the administration of medical care programs; to supervise and evaluate these programs as carried out by local welfare departments, and to determine the eligibility of persons to receive medical assistance for disability from the state.

The failure to place all these responsibilities under one person reduces effective planning and requires the Commissioner without medical training to carry out any necessary coordination.

This is the department that will be given an estimated $90 to $100 million annually to disburse for a program of medical care for the needy elderly with an eligibility requirement.

As yet only fourteen states have enacted legislation for medical care of the needy aged to qualify for funds under Title VI; hence data on the operation of a program of medical care for the needy aged exclusively are not extensive. One state with a unique program has already provided an experience in furnishing medical care to the aged. Colorado has an Old Age Pension Medical Plan for which the State Department of Public Welfare is responsible. According to the press, it is currently piling up a deficit of $1.5 million annually. For the third time there has been an attempt to curb the cost of the plan and relieve the financial crisis. Apparently overuse of hospitalization with unwarranted admissions and prolonged stays are responsible for the plight. Since Blue Shield and Blue Cross administer the plan for the state, this record bears out the weakness of that type of organization in administration of the plan.

Furthermore, the Academy knows of few instances where a Department of Welfare can validly point with pride to the quality of a program of medical care under its aegis.

Apparently the sole reason for assigning the medical program for the needy elderly in New York State to the Department of Social Welfare was the requirement of eligibility. Since experience has indicated that determination of eligibility is likely to prove so costly that it will use up an excessive portion of available funds for medical care, the Academy believes that it becomes a self-defeating and unwarranted expenditure that threatens the medical care program. For this reason it favors elimination of the present type of determination of eligibility. It suggests that a new and much simpler method of determination of eligibility be devised that will be less costly to administer. This function could remain under the policy control of the Social Welfare Department, which administers determination of eligibility for a number of programs. But at that point the Academy believes that the Department of Social Welfare's authority over the program of medical care for the needy aged should end.

To go one step further, the Academy is of the opinion that all programs providing direct medical service or hospitalization—except those for psychiatric disorders—and granting approval of hospitals should be incorporated into an independent unit. In 1959 New York State spent about $64 million for medical care

for welfare recipients. This amount was more than that spent by any other state for medical care; it was about 14 per cent of the total spent in the United States. When expenditures for the medically indigent are included, the state spent more than $91 million for medical care in all public assistance programs during that year. This was a 326 per cent increase over 1951. The new program of medical care for the needy aged will add an estimated $40 million to the expenditures. In the aggregate these programs for medical care present such a specialized responsibility and have become of such magnitude that they constitute a primary enterprise requiring operation as a regular but separate unit of the state government under the authority and direction of qualified physicians.

The Academy would emphasize that in the administration of a program of medical care for the needy aged, authority and responsibility should not be separated. It should be organized as an internally autonomous unit completely directed and controlled by physicians; it is most important that it have standards and regulations; and it is equally essential that its operations be supervised. The Academy is of the opinion that the Department of Social Welfare is not qualified to administer a program of medical care for the needy elderly in accord with these specifications.

Rather than defer comment until the proposed program has been in operation long enough to yield results, The New York Academy of Medicine believes that its misgivings are sufficiently well-founded that it should present them at this time. Above all, it is desirous that the new law should succeed. In this spirit it holds that increasing the chances of success by constructive action at an early stage is better than correction of failure.

MEDICAL EXAMINERS FOR NEW YORK STATE*

REPORT BY THE

COMMITTEE ON PUBLIC HEALTH**

THE NEW YORK ACADEMY OF MEDICINE

Dr. Alfred A. Angrist, Chairman of the Subcommittee on Medical Examiner Systems and Autopsy Law, the New York State Association of Approved Laboratories, submitted on behalf of the Association two problems for consideration by the Committee on Public Health:

1. The authority of the coroner and the medical examiner to perform an autopsy without consent of next of kin during the course of his duties.
2. Establishment of a medical examiner system throughout New York State to replace the present county coroner system.

Concern about these problems was precipitated by a legal action brought by one Dorothy Brown to recover damages on the claim that one of the coroners of Broome County performed an unauthorized and illegal autopsy on the body of her deceased husband. The case was tried in the County Court before a county judge and a jury on March 9 and 10, 1959; the jury returned a verdict in favor of the plaintiff for the sum of $3,500.00. Following the verdict the attorney for the defendant moved to set it aside on the grounds that it was against the weight of evidence, contrary to law, and was excessive.

The following account of the case is taken from Presiding Judge Brink's written decision:

> "This cause of action arose out of an incident which happened on the 10th day of February, 1958 when one Francis Brown, the deceased husband of the Plaintiff Dorothy Brown, was found dead in the Delaware and Hudson Railroad yards in the City of Binghamton, New York with his left hand partially severed. The deceased had been employed as a trainman by the Delaware and Hudson Railroad and reported for work shortly before midnight. The train on which he was to work was being assembled in the yard and was scheduled to leave some time later in the early hours of the morning. The decedent's body was found between two tracks in the railroad yards some time between 2:30 A.M. and 3:00 A.M. Dr. Vincent Maddi, one of the coroners of Broome County, was summoned and when he arrived the body had already been removed to the yard office. The widow was notified of the accident by the police,

* Report prepared by a Subcommittee comprised of: Robert W. Laidlaw, M.D., Chairman; Alfred E. Fischer, M.D.; Maximin DeM. Touart, M.D.; Peter Vogel, M.D., and H. D. Kruse, M.D., Secretary.

** Approved by the Committee on Public Health, November 7, 1960.

and when she learned that the coroner had directed an autopsy on the body, she protested to the police stating that she did not want an autopsy performed. The coroner testified on the examination before trial, that he did not recall whether before the autopsy he was advised as to the widow's attitude, but that it would not have made any difference.

"The autopsy findings showed: early acute myocardial infarction of left ventricle of the heart; together with, coronary atherosclerosis; old myocardial infarction of left ventricle; extensive trauma to left hand, with loss of soft tissue and bones; and ecchymosis over left side of chest. The coroner filed a decision stating that death was due to natural causes.

"The record shows, that there was no written request for an autopsy from duly constituted police authorities and further that no formal inquest was held involving the swearing and examining of witnesses. The principal issue of law involved in this case is the question whether under the circumstances the autopsy which the coroner caused to be performed upon the body of the deceased was authorized and lawful under the statutes of the State of New York authorizing and permitting dissection of a body of a deceased person.

"Under the Common Law, the body of a deceased person belongs to the nearest next of kin and no one had a right to mutilate or dissect a body without their permission. However, for the protection of society, it became necessary to authorize medical examiners to dissect bodies to determine the cause of death, particularly, in cases involving suspected crime and suicide. In most of the counties of this State, coroners are elected to act as medical examiners to investigate the cause of sudden deaths pursuant to authority vested in them by statute."

* * * * *

"It should be observed in the first place that Section 662 of the County Law charges the coroner with the duty of making inquiry into unnatural deaths. Section 773 of the Code of Criminal Procedure sets forth the conditions under which a coroner is authorized by law to hold an inquest upon a body. A close examination of this last Section is of considerable interest and, particularly, the phrase, 'under such circumstances, as to afford a reasonable ground to suspect that his death has been occasioned by the act of another by criminal means or has committed suicide.' . . . Black's Law Dictionary defines the word 'suspect' as follows: 'to have a slight or even vague idea concerning; not necessarily involving knowledge or belief or likelihood.' In other words, a coroner is authorized to hold an inquest, if there is even a slight possibility that the death of the decedent resulted from either crime or suicide.

"Section 4210 of the Public Health Law, Subdivision #2 authorizes a coroner to dissect a body whenever a coroner is authorized by law to hold an inquest upon a body. It should be noted that this statute does not provide, whenever a coroner holds an inquest upon a body, but rather 'when a coroner is authorized to hold an inquest upon a body.' The Attorney for the plaintiff

argues that a coroner does not have the right to dissect a body under this provision of the statute unless he actually holds a formal inquest. To this Court, it seems such an argument is unsound. It would seem ridiculous that a coroner should be required to swear witnesses and take proof before he first ascertained that the decedent died from unnatural causes and the cause of the traumatic death. To act otherwise, would cause unnecessary inconvenience and waste of time, not only for the coroner, but also for the witnesses who would necessarily be subpoenaed. A more reasonable interpretation of the intention of the statutes would be to say, that under any circumstances where a coroner suspects that a crime or a suicide is involved, he has the right to perform an autopsy as a preliminary part of an inquest, so that he may determine whether further investigation is necessary.

"In order not to interfere with burial plans and also for scientific reasons, post mortem examinations of bodies should be conducted promptly after death. They should not be delayed pending other types of investigations.

"With this construction of the statute, the only remaining question is whether under the facts and circumstances present in this case, the coroner was justified in suspecting that a crime might have been committed, or the decedent may have died as a result of suicide. The Plaintiff's husband was found dead under unusual circumstances. He was lying between two railroad tracks with a portion of his hand severed. Before the coroner arrived, the body had been moved. No one saw the decedent die or knew how he died.

"Under all the circumstances of this case, it is the opinion of this Court, that as a matter of law, the coroner was justified in suspecting violence. To hold otherwise, in the opinion of this Court, would be dogmatic and arbitrary interference with the functions of a medical examiner. Unfortunately, the dissection of a human body often adds to the sorrow and anxiety of the next of kin. However, in our modern society with the ever increasing numbers of traumatic deaths, it seems most important that our Courts should give the statutes involved a broad and liberal construction."

* * * * *

In a deposition admitted as testimony during the trial the coroner stated that the partly amputated hand on the decedent raised the question whether it or something else was the cause of death. Furthermore, loss of part of the hand could have been criminal or accidental. For these reasons he ordered an autopsy. On direct examination he testified that an autopsy would not disclose whether death was homicidal, suicidal, natural, or accidental. It would give information on the cause of death. He reiterated his opinion which he had filed on his report that death was from a heart attack resulting from coronary occlusion and acute myocardial infarction. In his judgment the injury to the hand occurred after death.

On cross-examination it was brought out that the autopsy report by the pathologist stated that death could have ensued in the absence of immediate medical attention as the result of hemorrhage. Disagreeing with the pathologist's opinion, the

coroner reaffirmed his position that death was due to natural causes, not trauma or accident.

The presiding judge of the County Court set aside the jury verdict, granted defendant's motion for nonsuit and dismissed the plaintiff's complaint. The plaintiff then carried an appeal to the Appellate Division, Third Department, Supreme Court, State of New York. There the presiding county judge's decision was reversed.

The opinion for reversal by the Appellate Division, written by Presiding Justice Bergan, follows in part:

> "The statutory test of the right of a coroner to order an autopsy under circumstances such as those in this case is whether he 'has reasonable ground to suspect' that the death was occasioned 'by the act of another by criminal means' or that decedent is a suicide (Code of Criminal Procedure, § 773, read with Public Health Law, § 4210).
>
> "Whether in the case of a railroad or other industrial worker found dead near dangerous machinery or devices which could, and often do, accidentally cause death, a coroner would have 'reasonable ground to suspect' a crime would depend on the circumstances and the reasonableness of such ground would usually be a fact question for the jury.
>
> "On the trial of this case the judge treated the problem as a question of fact and carefully submitted it for the jury's verdict. On the motion to set aside the verdict the judge held as a matter of law that the coroner was 'justified in suspecting violence'; and ruled that a coroner has the right to direct an autopsy where he 'suspects that a crime is involved.'
>
> "The statute does not rest a discretion to direct autopsy in the mere mental 'suspicion' of the coroner. He must, says the statute, have 'reasonable ground' to suspect a crime. The rational basis of suspicion that a crime has been committed is the test; and not merely 'violence' which often is a concomitant part of an accident. On this record the question is one of fact and not of law and the complaint should not have been dismissed.
>
> "The defendant moved to set aside the verdict as against the weight of evidence and as excessive. The court did not pass on these motions because the judge granted the motion to dismiss as a matter of law.
>
> "We should determine these motions thus left open rather than remit the action to the County Court for their determination (Civ. Prac. Act, §§ 584, 626; *Mysliwiec v. W. Lowenthal Co., Inc.*, 280 App. Div. 1001; *Guido v. Delaware, Lackawanna & Western R.R. Co.*, 5 A. D. 754).
>
> "The verdict is not against the weight of evidence; nor does it seem in our judgment so far excessive as to require a new trial on this ground."

* * * * *

> "The judgment should be reversed on the law and the facts and judgment entered for plaintiff in accordance with the verdict with costs to appellant."

Upon receiving this reversal, the original defendant, Broome County, took the

case to the Court of Appeals of New York State. There the Appellate Division's decision was sustained.

Here in part is the Court of Appeals' opinion, written by Justice Burke:

"The trial court set aside a verdict of a jury and dismissed the complaint as a matter of law in this action brought against the County for an alleged unauthorized autopsy performed at the direction of a coroner, over the objections of the plaintiff, on the body of her husband. . . . The Appellate Division has reversed the judgment on the law and the facts, and directed judgment for the plaintiff, finding that under the circumstances of this case the statutory standard of § 773 of the Code of Criminal Procedure (i.e. reasonableness of the coroner's conduct) was a fact question for the jury.

"The appellant's principal argument that the reasonableness of the conduct herein is simply a question of law misconstrues the meaning of the statutes. Although the statutes governing the performance of autopsies grant broad discretion to coroners, the power is limited to deaths which indicate a possibility of criminality or suicide. The exercise of such discretion will generally be upheld because it is apparent that a court, in most cases, can readily determine whether the coroner had 'reasonable ground to suspect' that the death was occasioned 'by the act of another by criminal means' or that decedent is a suicide. (Code of Criminal Procedure § 773, read with Public Health Law § 4210.) Occasionally a court may find that the evidence shows an abuse of discretion as a matter of law but such instances are rare. There are, however, many cases, and this is one, where the question of the reasonableness of the grounds for directing an autopsy may not be found to be absolutely right or wrong. It falls in an area where there is a want of full proof. Then the question of reasonableness cannot be treated as a problem of law alone. When, as here, the nature of the work, the duties of the deceased, the site of the work and the scene of death disclose conditions which often accompany accidents resulting in death, there should be substantial reasons present to justify the need for an autopsy. Since the death was unwitnessed and could have been caused by the injury to the hand, an autopsy would not lead to signs of criminality or point to a suicide. When these facts are considered collectively, the judgment used by the coroner cannot be found to be unassailable. In such circumstances an appraisal of the sensibleness of a decision directing an autopsy does involve a finding of fact."

* * * * *

"The judgment of the Appellate Division should be affirmed. . . ."

In reviewing the case it should be noted that two actions may have affected the course of legal events:

The first has to do with the coroner's decision in his written report in the performance of his duties. From the circumstances surrounding the death of Francis Brown and the findings upon autopsy two causes of death were to be considered: 1) a coronary attack; 2) hemorrhage from a partially amputated hand. Further to

be decided was whether the circumstances were homicidal, suicidal, natural, or accidental. It was the coroner's opinion that a natural death from a coronary attack had occurred and that partial loss of the hand had been a subsequent occurrence. This opinion differed from that of the pathologist. In such circumstances some medical examiners would take the view that it would be difficult if not impossible to be so categorical. Whether with a different report from the coroner the plaintiff would have taken legal action can only be surmised. This point is not an issue in the judicial review, and is broached only to emphasize the sometimes difficult problems that confront the coroner or medical examiner and require the highest professional skill in forensic medicine.

Secondly, the counsel for the defense moved to set aside the original verdict as against the weight of evidence and as excessive. The presiding judge granted the motion to dismiss as a matter of law without passing on the grounds advanced for the motion. In retrospect it is tempting to speculate on the outcome of the case if counsel had moved to dismiss on the grounds of the law. To be sure, it is not certain that even then the Appellate Division would have upheld the presiding judge. For, in the written opinion of the latter body, it passed on the two motions having to do with weight of evidence and excessive award and reversed the judgment on both facts and the law.

There is always the possibility that a legal case may be lost on technicalities that bear no relation to the merits. In this case it should be borne in mind that the adverse ruling handed down by the Court of Appeals may become a precedent. Dr. Angrist has pointed out the possibility of catastrophic consequences from such an outcome: the effect on medico-legal investigations of deaths in the State will be extremely serious. He further adds that requiring consent introduces the existing ambiguity in the law in which it is not certain whether permission from all of equal rank among next of kin is required.

Since the higher courts handed down an adverse ruling, the presentiment about medico-legal investigations in the State makes a new law imperative in order to avoid chaos. For, in the light of the precedent established by the decision of the Court of Appeals, the existing law does not seem to confer adequate, unmistakable, and assured authority to order an autopsy without jeopardy of litigation.

The difficulty is in the wording of the existing law. The troublesome and disputatious words in the law are "reasonable ground to suspect a crime". The Appellate Division made this phrase the critical issue so far as interpretation of the law was concerned. It is manifest that such phraseology raises a debatable issue and almost invites litigation. Equally disturbing is the interpretation put on the law by the Appellate Division. In his brief submitted to the Appellate Division, the County Attorney advanced the following argument under "Point I. The autopsy was legally ordered":

> "Facts and circumstances for this case is [sic] set forth in the record to show that the deceased was found under circumstances that a coroner would be justified in holding an inquest. The deceased was found lying between the railroad tracks with his left hand partially severed and had been removed from

> the tracks to a shed in the Delaware and Hudson Railroad yards in the City of Binghamton, New York, before coroner arrived. No one saw decedent die or knew how he died. These circumstances appear to be sufficient to justify a coroner to suspect violence."

But the Appellate Division and the Court of Appeals did not concur with the County Attorney in this view.

It would appear that the situation would be much improved by a new and clearer law. At present it almost seems as if the legality of ordering an autopsy depends on what it reveals. When an autopsy, especially one ordered on slight suspicion, turns up valuable and critical evidence, it is tacitly accepted as justifiable, indeed essential. On the other hand, when it adds little material evidence, it is open to the charge of being unnecessary. The fact is that after an autopsy has been completed, it is always immeasurably easier to decide whether it has been absolutely necessary. But the coroner or medical examiner must make his decision without the benefit of after-knowledge. What should not be forgotten is that the long history of forensic medicine has contained instances in which the autopsy, ordered on very slight suspicion, has revealed unexpected and unsurmised facts. Furthermore, it should be emphatically noted that on occasion bodies have had to be exhumed for autopsy, a development which illustrates how elusive suspicion may be. In view of these considerations and of the purpose of the autopsy to serve the ends of justice, it would seem wise in case of doubt or uncertainty to proceed on the assumption that an autopsy may provide material evidence. Indeed, it is most often needed under such circumstances. The conclusion is therefore inescapable that the coroner or medical examiner, who functions impartially as an independent officer, should be clearly directed and empowered to pursue his duties without the threat of possible litigation. Yet it is not just that the immunity of the coroner is in question that points to the need for revision of the existing statutes; justice dictates such a step.

To be more specific, one proposed remedy to the situation would seem to be a legislative amendment that would require the coroner to have an autopsy conducted in every sudden and unexplained death unless consideration of the surrounding circumstances and physical examination of the body renders such a course unnecessary. In view of the number of times that a seemingly accidental death has been later demonstrated to have been criminal, this proposed amendment does not seem unreasonable. It should be borne in mind that the medical examiner's function is to determine the cause of death, which in one instance may bring out unsuspected criminality and in another case may show what had at first glance appeared to be criminal violence was actually accidental trauma. On account of the purpose of the autopsy and its valuable function as a source of evidence, the Committee believes that when a death occurs in a suspicious, questionable, unusual, or uncertain manner, the ordering of an autopsy by the coroner or medical examiner should be mandatory, except that waiver of it by that official should be discretionary.

On the second question raised by Dr. Angrist, namely, establishment of a medical examiner system throughout New York State to replace the present county coroner system, the Committee on Public Health can draw upon its long experience.

The shortcomings of the coroner system are not a new subject nor are they strange to the Committee. It is a national problem fully documented in an extensive bibliography. By request the Committee participated in the deliberations that attended the replacement of the coroner system by the Medical Examiner's Office in New York City in 1915. Thus, it is familiar with the duties and professional requirements associated with the investigation of sudden and unexplained deaths. It has presented its views on the specifications for medical examiner. Despite the advance registered by the conversion to the medical examiner system in a few counties, the Committee has striven for even greater progress. For one thing, as the result of its deliberations it realized many years ago that forensic medicine was a highly significant and key subject in the investigation of unexplained deaths, that the subject was accorded inadequate recognition in the medical curriculum, and that an insufficient number of physicians were trained in it. Since 1927 the Committee has at every promising opportunity drawn attention to these inadequacies, and has by reports and action attempted to overcome them by encouraging establishment of courses in forensic medicine.

Through the years the concept of the duties of the coroner's office has undergone transformation. Once the coroner was mainly a special magistrate with responsibility for investigation and gathering of evidence on sudden and unexplained deaths. It was and still is an elective office held as often as not by a layman. Since the major duty of the office was to ascertain the cause of death and the attending circumstances, it became apparent that a physician was best fitted for this responsibility. Then the growth of pathology as a specialty and the increasing recognition of the importance of the autopsy in providing evidence brought prominence to that part of the investigative procedure. Where the coroner system still prevails, a pathologist, if available, is apt to be requested to conduct any necessary autopsy. On the other hand, it should be pointed out that the pathologist, in conducting the postmortem examination, performs only one, not all, of the functions that are an essential part of the investigation of sudden and unexplained deaths. In the medical examiner system it is usually specified that the official be both a physician and a pathologist. But these specifications still fall short of enumerating an essential part of his training for effective performance of his duties: criminal investigation and forensic medicine. It is not enough that the medical examiner be a physician and a pathologist. He must have training in consideration of all the circumstances surrounding sudden or unexplained death. In short, the duties of the official with this responsibility require that he be a combination of physician, pathologist, and criminal investigator.

In view of the fairly substantial number of sudden and unexplained deaths in modern society, and the need for highly specialized knowledge and skill in investigation of them, the Committee on Public Health recommends that the medical examiner system replace that of the county coroner system throughout New York State. In the opinion of the Committee any plan to replace the coroner by the medical examiner should specify the special training the latter should have. In addition to his degree in medicine he should have graduate training in pathology,

and courses in criminal investigation and forensic medicine.

In making this recommendation the Committee has been realistic in recognizing the difficulties in achieving it. It is cognizant of things as they are while pointing out how they should be. It is aware of the shortage of medical examiners with such qualifications. It realizes that if the medical examiner system was instituted throughout the state, probably few counties could immediately fill the office with trained men. The Committee believes that this situation could be overcome by proper encouragement of hospital pathologists, who hold a medical degree, to take necessary courses and training in forensic medicine that would qualify them as medical examiners. A standard manual of procedure, such as has been promulgated for the Chief Medical Examiner of the City of New York, will also be helpful in the investigation of unexplained deaths in the counties.

To replace the coroner system by a medical examiner system in New York State would require enactment of new legislation or utilization of a provision in the present law. In 1951 the state legislature passed a law amending the coroner system with the effect that the office might be abolished and a medical examiner system created by referendum.

Summary of Recommendations

The Committee on Public Health recommends that:

1. Necessary action be initiated to replace the county coroner system by the medical examiner system throughout New York State.

2. An amendment to the existing law should be sought which would be designed to clarify the existing provision granting the coroner a right to order an autopsy in the investigation of unexplained deaths.

NEW YORK HEART ASSOCIATION

Scientific Session on Research held at The New York Academy of Medicine, April 19, 1961

ABSTRACTS OF PAPERS

*Current of Injury, Primary Etiologic Agent in Vascular Occlusion?**

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In 1952 investigators first indicated that applied oriented electric currents resulted in vascular occlusion. With the field oppositely oriented, vascular occlusion can be delayed in damaged vessels. Reversal of the normal measured transmural potential of a dissected aorta (intima-negative to intima-positive) usually heralds intravascular occlusion. Recent experiments show that currents in the range of 5 to 20 microamperes will occlude the visualized vessels of the rat mesentery, as will the injury currents from an injured bit of rectus muscle placed beneath the visualized mesentery.

A hypothesis has evolved which states that the blood-vessel wall probably expends energy neutralizing adventitious currents and currents of injury from surrounding injured tissues. In order to do this the blood-vessel wall must control ion transport across the blood-intimal wall interface.

Recent experiments measuring sodium and chloride fluxes across the aorta and vena caval wall give evidence that the large vessel wall *does* in fact expend energy in the active transport of sodium and chloride at least in part to maintain electric neutrality across the blood intimal interface. The discussion will present detailed information from these experiments relating to the possibility that vascular occlusion in vessels may occur when they lose the ability to maintain the normal transport mechanisms.

* Presented at the *Scientific Session on Research* of the New York Heart Association, Inc., held at The New York Academy of Medicine, April 19, 1961.

** Past Grantee, New York Heart Association.

*Toxic Effects of Ouabain on Purkinje Fibers and Ventricular Muscle**

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Ventricular arrhythmias of several types are a common sign of digitalis toxicity. Whether the foci from which these arrhythmias originate are located in the specialized conducting system, in the ventricular muscle, or both tissues has not been demonstrated. In an attempt to clarify this point, the toxic actions of ouabain have been studied on single Purkinje fibers and single ventricular muscle fibers by means of the micro-electrode technique.

* Presented at the *Scientific Session on Research* of the New York Heart Association, Inc., held at The New York Academy of Medicine, April 19, 1961.

** Past Grantee, New York Heart Association.

False tendons and trabeculae carneae or small papillary muscle were perfused with Tyrode solution at 37°C. Tissues were stimulated at the rate of 60/min. throughout the experiment. Two duplicate baths, each containing a preparation of Purkinje fibers and ventricular muscle, were employed. One tissue bath served as a control. In the other bath, after an initial record of transmembrane potentials of the tissues was obtained, ouabain was added to the perfusion fluid in the reservoir to reach a final concentration of 1:8,000,000.

Signs of toxicity developed much earlier in the specialized conducting fibers and consisted of a reduction in amplitude and duration of the action potential and increased depolarization during phase 4. In most Purkinje fiber preparations extrasystoles and rapid spontaneous rhythm developed and resting potential decreased. Ventricular muscle fibers showed a decrease in the plateau and in the magnitude of the action potential. The resting potential was decreased to a lesser extent. These changes in the muscle occurred much later than did the changes in the Purkinje tissue. Spontaneous depolarization was not observed.

In another series of experiments the effect of contraction on development of ouabain toxicity was investigated. Signs of toxicity appeared earlier in the muscles driven at constant rate than in duplicate quiescent muscle. Higher rates of stimulation reduced further the interval required for the appearance of signs of ouabain toxicity.

*Direct Adrenocortical Stimulatory Effect of Serotonin**

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It has been shown that serotonin, when added to mammalian adrenal slices incubated *in vitro*, produces an increase in blue-tetrazolium reacting material, the nature of which has not been further identified (Rosenkrantz, H. *Endocrinology 64*:355, 1959). Monsour and associates (*J. Biol. Chem. 235*: 466, 1960) have recently demonstrated that serotonin stimulates the production of adenosine 3′, 5′ monophosphate in the liver fluke. Since it has been well established that 3′, 5′ AMP is a potent activator of liver, muscle and adrenal cortical phosphorylases, and since previous work from our laboratory has shown that 3′, 5′ AMP will stimulate the synthesis of cortisol, the present set of experiments was designed to investigate the effect of serotonin on adrenal steroidogenesis *in vivo*.

By means of direct arterial perfusion of the adrenal glands of the hypophysectomized dog, it was found that serotonin stimulates the secretion of cortisol, reaching levels (5 μg/min.) equal to those following ACTH. Also, serotonin, like ACTH, seemed to result in higher than normal secretion rates of aldosterone (0.038 μg/min.).

The serotonin stimulatory pattern *in vivo* resembled that seen after the infusion of AMP and ACTH and suggests that serotonin may act via the same common pathway. On the other hand, the serotonin precursor, 5-OH tryptophan, does not have this stimulatory activity. Furthermore, it was found that reserpine, which releases serotonin from CNS tissue stores, has no direct stimulatory effect on the adrenal cortex.

Thus, serotonin seems to be the fourth compound which stimulates adrenocortical steroidogenesis, the others being ACTH, vasopressin and 3′, 5′ AMP.

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*The Effect of Temperature Changes of the Blood on the Pulmonary Circulation**

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There is a large volume of literature dealing with the effect of hypothermia on the systemic circulation, but few studies have concerned themselves with its effects on the pulmonary vascular bed. With the widespread use of hypothermia, this aspect may be of greater practical importance than has hitherto been recognized. Analysis of the vascular effects of hypothermia is made difficult in the intact animal because of the profound changes which occur in the heart itself. The present study, therefore, makes use of the technique of separate perfusion of the systemic and pulmonary circulation by means of two extracorporeal pumps which allow changing the temperature of the blood in the one circuit while that in the other is kept constant.

When the temperature of the blood in the pulmonary circuit of a normal dog was changed from 38° to 20° C., pulmonary artery pressure rose and systemic blood pressure dropped. Since the blood flow remained constant in both the systemic and pulmonary circuits, the response was interpreted as a result of changes in resistances in the respective vascular beds. The opposite result was recorded on changing the temperature of the pulmonary perfusate from cold to warm, i.e., pulmonary pressure dropped and the systemic pressure increased.

The effect on the pulmonary vascular bed confirms the findings of earlier investigators, but the fall in systemic blood pressure has not, to our knowledge, been reported previously. Whereas the changes in the pulmonary vascular bed were due to the direct effect of temperature changes on the pulmonary vascular musculature, the response of the systemic circulation proved to be reflex in nature. It could be abolished by cutting of the vagi and by the administration of a sympathicolytic drug into the systemic circulation, but it was not abolished by atropine.

It was, therefore, concluded that we are dealing with a reflex mechanism which originates in the pulmonary vascular bed, the afferent pathway of which is transmitted by the vagus, whereas the efferent pathways are found in the sympathetic nerves.

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*Renal Function After Intracardiac Operations Involving Total Body Perfusion**

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Twenty patients were studied one day before and three days after repair of congenital cardiac malformations, utilizing total body perfusion. Details of pre-operative and postoperative management were identical except for the fluid prescription. Interest was focused upon renal function in general and upon handling of water and electrolytes in particular.

Patients of comparable surface area undergoing operations of comparable severity were paired. One group received an infusion of electrolyte-containing fluids in amounts calculated to replace insensible water loss, urine, blood and external gastrointestinal losses. The second group received an infusion containing 5 per cent glucose in water in amounts of 500 ml/M.²/24 hours during the first day, and 750 ml/M.²/24 hours during the second and third days.

The following determinations and calculations were performed: 1) clearances of urea, total osmolality, solute-free water, sodium, potassium and chloride; 2) urine/plasma ratios of urea, total osmolality, sodium, potassium and chloride; 3) 24-hour urinary output of urea, total osmolality, ammonia, titratable acid, sodium, potassium and chloride; 4) total plasma CO_2 and pH of arterial blood.

The results indicated that clearance, U/P ratio and 24-hour elimination of urea dropped in both groups during the first two days. Clearances, U/P ratios and 24-hour elimination of total osmolality, sodium, potassium and chloride as well as 24-hour urine output were consistently higher in patients in the first group.

Electrolytes, in amounts given, were well tolerated and excreted in the study period. There was no clinical evidence of an expanded extra fluid compartment in these patients. Renal function was not fixed in either group of patients; adjustment to the type of fluid administered occurred within limitations. Renal compensation for acidosis was effective in both groups, but blood pH returned to normal more rapidly in patients receiving electrolytes. Some patients receiving electrolyte-free fluids eliminated large amounts of electrolytes in the urine; they were potential candidates for water intoxication.

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*Uptake of Triglycerides by Polymorphonuclear Leukocytes**

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The manner in which ingested fat disappears from the circulation is still largely unknown. It has been proposed that removal of chylomicrons occurs by a process resembling phagocytosis. The present study was carried out with polymorphonuclear leukocytes obtained from rabbit peritoneal exudates. These cells readily phagocytize *in vitro*, therefore uptake of complex molecules can suitably be examined with this cell system as a model for our study.

The results suggest that uptake of fat occurs in the un-esterified form only.

Preceding studies have shown that polymorphonuclear leukocytes rapidly incorporate into cell lipids, ^{14}C-1-labeled fatty acids present in the medium. Virtually all fatty acids incorporated were recovered as fatty esters, both phospholipid and non-phospholipid. Since the energy required for uptake is derived from anaerobic glycolysis which also provides glycerophosphate and its derivatives for ester formation, the possibility was considered that esterification may be involved in the mechanism of entry of fatty acids into the cell. These studies were extended to determine whether complex fat molecules are also taken up by the leukocytes. ^{14}C-1-labeled tripalmitate or tristearate was homogeneously dispersed in a suspension of leukocytes in ascitic fluid and the partition of label between cells and medium determined under different conditions. Much radioactivity was found in association with cell lipids. This association occurred to the same extent during incubation at 37°C and at 4°C and was not affected by the time of incubation, nor by inhibitors which markedly suppressed uptake of non-esterified fatty acids. Moreover, all radioactivity remained in the triglyceride fraction and none was recovered as $^{14}CO_2$, water-soluble breakdown product or as phospholipid.

These results are taken to indicate that labeled triglycerides are not incorporated into cell lipids nor metabolized. It is postulated that lipolysis must precede entry of lipid into the cell.

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** Senior Research Fellow, New York Heart Association, Inc.

*Quantitative Morphologic Studies on the Dimensions of the Alveolo-Capillary Membrane**

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In an attempt to improve on the current concepts of the structures involved in pulmonary diffusion, the alveolo-capillary membrane is defined as a tissue space with an external and an internal boundary: the air-tissue and the tissue-blood interfaces. In order to estimate the extent of these two interfaces we have determined the size of the alveolar surface and of the alveolar capillary surface by morphological methods on cadaver lungs. A rigorous standardization of the techniques has allowed conversion of the measurements obtained on histological preparations into the fresh state.

The air-tissue interface was found to be dependent on the lung size. For a lung volume of 7 liters, for example, it amounts to 75 m^2. The tissue-blood interface was found to be of the same magnitude as the air-tissue interface, being, in addition, dependent on the degree of filling of the capillaries. As incidental findings, the total number of alveoli in the lung appeared to be constantly 300 million despite a more than twofold variation in the size of our lungs. The volume of the capillary bed was estimated to measure approximately 200 $cm.^3$ at a total lung capacity of 7 liters, and at an average degree of filling of the capillary bed. This morphologically estimated capillary volume appears to be more than twice the physiologically estimated "pulmonary capillary blood volume" usually given.

The complete quantitative definition of the new concept of the "alveolo-capillary membrane" requires, in addition, quantitative studies of the variation in thickness and structure of this tissue space. It is anticipated that this will lead to a more anatomically oriented definition of the "pulmonary diffusing capacity", useful both in normal and pathological conditions.

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Just the mechanics of learning what is being issued constitutes no small task. The records of newly published books are checked constantly. Much is published, however, which is not listed in these sources, and to find notices of these "non-trade" books and pamphlets is much more time-consuming. Some fifty periodicals are gone over regularly for book reviews, announcements, or casual mention of publications which we should fail to hear of otherwise.

Even so, there is a large class of material which is important for a library like the Academy's but which is missed more often than not. This is composed of books and pamphlets for which organizations are their own publishers, and of which, therefore, no mention is made in the usual trade channels. Examples of this type of publication are:

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Most of such material consists of pamphlets, printed or mimeographed, and has therefore only an ephemeral existence. It goes usually only to members of the organizations issuing it, and after they finish with it, it goes into their waste-baskets. Some societies refuse to distribute to non-members abstracts of their proceedings, transactions and membership lists even when appearing as sections of a periodical the rest of whose issues are freely sold. A great deal of all this is of historical value, some of it is of present clinical significance, and some of

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Rush, Benjamin. *Medical Inquiries and Observations upon the Diseases of the Mind.* Philadelphia, Kimber & Richardson, 1812. With an introduction by Dr. S. Bernard Wortis.

Corvisart, Jean Nicolas. *An Essay on the Organic Diseases and Lesions of the Heart and Great Vessels.* Boston, Bradford & Read, 1812. With an introduction by Dr. Dickinson W. Richards.

Laennec, René Théopile Hyacinthe. *A Treatise on the Diseases of the Chest.* London, Underwood, 1821. With an introduction by Dr. Paul Klemperer.

Heberden, William. *Commentaries on the History and Cure of Diseases.* London, T. Payne, 1802. With an introduction by Dr. Paul Klemperer.

Charcot, Jean Martin. *Lectures on the Diseases of the Nervous System.* Delivered at La Salpêtrière. 2. ser. London, New Sydenham Society, 1881. Introduction by Dr. Walter Riese.

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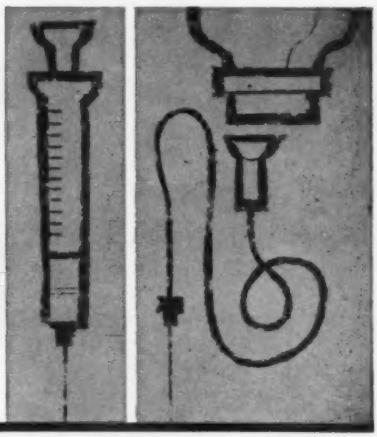

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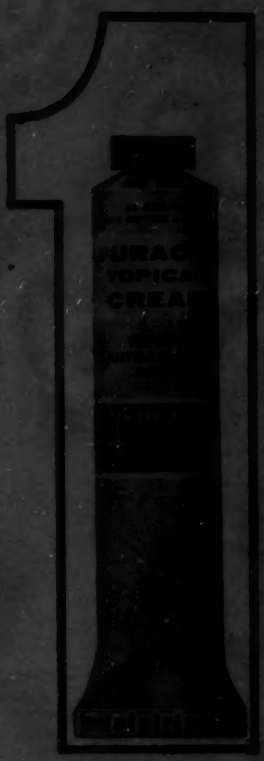

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